395

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.

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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.[1] Recently, evidence has been presented suggesting a deficiency of another enzyme in tyrosine catabolism, fumarylacetoacetase (4-fumarylacetoacetate fumarylehydrolase. EC 3.7.1.2). in this disease.[2] Tyrosinemia and tyrosyluria can be found in liver disease due to other causes, notably. hereditary fructose intolerance.[1, 3]

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, 6] 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-hydroxyphenyllactic 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.

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

	Normal values	On regular diet 5-6 mo of age (N = 3)	On restricted diet 6 mo 9½ yr (N = 52)	1 wk prior to transplant on restricted diet (N = 1)	2 days after transplant (N = 1)	0.5-11 wk after transplant (N = 7-10)	12 wk after transplant (week prior to death)
Serum tyrosine (mg/dl)	Mean 2.47[7] SD ± 0.97	Mean 13.2	Range 0.7-6.3 Mean 3.29 SD ± 1.16	3.83	0.72	Range 0.59-1.25 Mean 0.79	1.1-1.2
Urine tyrosine (μmol/24 hr)	(3-12 yr)[10] Range 40-168			377.0	73.5	Range 62.5-223.0 Mean 136	46.8
Urine pHHPA and pHPLA (μmol/ml)	Range 0.0-0.3[10]	Mean 19.0	Range tr-24.0 Mean 2.62 SD ± 4.0	6.85	0	Range 0-0.16 Mean 0.11	0.19
Urine ALA (mg/liter)	Range 0.0-5.4[11] Mean 2.2	Mean 5.57	Range 3.0-37.0 Mean 20.5 SD ± 3.34	34.4	3.48	Range 3.1-10.0 Mean 4.94	9.4
RBC ALA-D (μmol ALA/min/liter RBC)	Range 22.4-44.5[12] Mean 33 SD ± 4.8		Mean <6.0 N = 20				
RBC protoporphyrin (μg/dl)	Range 22.0-87.0[13] Mean 46.0 SD ± 14		Range 84.0-95.0 Mean 93.3 SD ± 10.4 N = 3				

Abnormal liver function tests included clotting studies uncorrected by vitamin K. Metabolic studies revealed hypertyrosinemia, tyrosyluria, 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/kg/day, phenylalanine 41 mg/kg/day, and protein 2.1 gm/kg/day. Growth measures at the last outpatient evaluation at 9⁹⁄₁₂ 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 trauma 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/ng ml (normal < 2.0/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 II. Demonstration of normal aldolase activity in patient's native liver after hepatectomy*

Liver	Substrate		
	Fructose-1, 6-diphosphate	Fructose-1-phosphate	FDP/F-1-P
Control	26.7	22.0	1.2
Patient	37.4-43.5	30.2-26.8	1.2-1.6

*Enzyme activity is expressed as nanamoles NAD formed/mg protein min at 37° utilizing the assay of bolstein and Rutter.[16]

Table III. Zinc concentrations in urine, plasma, and red blood cells

	Normal[17]	Period 1974-1975		
		Range	N	Mean
Urine zinc (mg/24°)	0.4-0.6	0.006-0.05	5	0.036
Plasma zinc (µg/ml)	0.89 ± 0.13	0.64-0.58	2	0.61
RBC zinc (gm/ml)	10.1 ± 1.2	10.7-15.4	2	13.0

reserpine and hydralazine therapy. Four days postoperatively she had symptoms of left-parietal occipital infarct, but there were no permanent residua. Beginning on the fifth postoperative day and extending until her preterminal deterioration nine weeks later, she was allowed a diet unrestricted in quality and quantity. Following transplantation, serum tyrosine concentrations, all but one urinary examination of urine tyrosine values, and all measurements of urinary and tyrosine metabolites were within normal limits (Table I). She was walking within two days after surgery. She was active and allowed to spend the weekends out of the hospital, participating in multiple activities for two months.

Four weeks postoperatively she had her first rejection episode, requiring increased doses of steroids. Bilirubin, SGOT, SGPT, and alkaline phosphatase values temporarily improved but never returned to prerejection levels. Contrast injection through the choledochojejunostomy stint revealed no obstruction to biliary drainage, and the stint was removed. Six weeks following transplant a percutaneous liver biopsy was performed because of persistently elevated hepatic enzyme values. This revealed mononuclear infiltration of the portal tracts with centrilobular cholestasis, compatible with partially treated rejection.

Ten weeks after transplant she developed abdominal pain with increasing ascites. She became febrile, and *Staphylococcus aureus* was cultured from her blood. A paronychia was drained. She was given cefazolin and gentamicin parenterally. All liver enzyme values rose rapidly but HB₂Ag remained negative. A repeat percutaneous liver biopsy performed 11 weeks postoperatively showed deterioration, with marked cholestasis and central and lobular necrosis.

With deteriorating hepatic function she developed encephalopathy. Because the encephalopathy did not respond to conven-

tional management, and clotting function was declining, an... exploratory operation was performed 12 weeks after transpla... tion. Portal vein thrombosis with suppurative pylephlebitis... discovered. Gram stain from the portal vein revealed gr... positive cocci in clusters. She had cardiac arrest during su... and could not be resuscitated. Autopsy revealed no new... ings.

METHODS

Serum tyrosine and phenylalanine determinations... performed according to the methods of Phillips,[7] a... McCaman and Robins.[8] Urinary tyrosine metabo... were determined by gas chromatography after form... methyl esters, using the diazomethane method.[9] Urin... tyrosine was quantitated by the method of Carver a... Paska.[10] Urinary delta-amino levulinic acid determi... tions were measured as reported by Tomokuni et al... ALA-dehydratase activity of red blood cells was al... determined.[12] Determinations of urine and plasma zi... were made by atomic absorption spectrophotometry,... following the specified collection procedure.[14] Protopor... phyrin of red blood cells was also determined.[15] Li... aldolase activity was measured spectrophotometrically... means of the coupled reactions described by Bolstein a... Rutter.[16] The laboratory results are summarized in Tabl... I to III.

DISCUSSION

This patient's presentation and physical and laborato... findings are typical of hereditary tyrosinemia, with... improvement of the metabolic studies after dietary restri... tion of tyrosine and phenylalanine.[5] Hereditary fruct... intolerance (hepatic aldolase deficiency) can present in... similar fashion,[18] but this patient's liver had nor... aldolase activity (Table II), and she responded bioche... cally to a diet restricted in tyrosine and phenylalanine... unrestricted in fructose. Although our patient did... have evidence of vitamin D-resistant rickets, she did h... intermittent porphyria,[19] elevated urinary ALA... es,[20,21] and evidence of ALA-D deficiency (Table I)... patient is among the first with tyrosinemia in wh... decreased red cell activity of zinc-dependent enzym... ALA-D, and zinc deficiency as measured by diminish... levels in plasma and urine, have been documented... (Table III). The appearance of hepatoma is characteris... of patients with hereditary tyrosinemia, even in the chil... treated with tyrosine and phenylalanine restricted die...

Hepatocarcinoma usually appears in children over t... age of 5 years; one third of the cases are associated w... cirrhosis[22]; 37% of patients with hereditary tyrosine... surviving beyond 2 years of age develop hepatocarci... ma.[4] The median age at the time of death has be... years, with a range of 4 to 25 years. Hepatoma was...

death in 66% of the females and 57% of the males. ...dence of tumor among patients with hereditary ...mia 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 ...%),[22] suggesting that factors other than the mere ...e of cirrhosis are associated with the induction of ...ma in tyrosinemia. The coexistence of cirrhosis and ...carcinoma also distinguishes the tyrosinemic chil-...m others with this tumor, since in contrast to ...this association is relatively infrequent in the ...c population.[24]

...a fetoprotein would not seem to be of diagnostic ...these patients, since this may be elevated in the ...of tumor,[25] and may be within normal limits in ...ence of hepatoma, as seen in this patient and ...g's.[5] Thus, isotopic liver scan might be considered ...routine management of patients with hereditary ...mia.

...ated hepatocarcinoma is uniformly fatal. The ...from the time of diagnosis of 47 untreated ...with primary cancer of the liver ranged from one ...24 months, with a mean of five months.[26]

...and McCary[26] reported a series of 47 pediatric ...who had been managed with surgical resection of ...carcinoma; 27 were alive, 15 without metastasis, ...even of these patients were well at least five years ...ng 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 ...rvival beyond five years of age.[22] Radiation and ...cer drugs usually had little effect on these hepatic ...ms; lobectomy, hemihepatectomy, or extended ...epactectomy were the operations of choice.[22] The ...odular cirrhosis of patients with hereditary tyrosi-...and hepatoma markedly increases the operative ...as in our patient, precludes surgical resection. ...ves in these patients are then to do nothing, to ...odalities (i.e., radiation and drugs) which appear ...positive benefit, or to consider liver transplanta-...

...the first liver transplantation in 1963, 119 have ...ported.[27-29] In one report, more than half of the ...were children.[28] Hepatoma was the most common ...for liver transplantation for adults, and second for ...[27, 28]

...ne replacement through orthotopic liver trans-...on for inherited metabolic disorders has been ...sly reported for Wilson disease (two patients), ...1-antitrypsin deficiency (one patient),[28] and for ...n-Pick disease (one patient).[29] These patients have ...remarkable one-year survival of 100% and success-

ful treatment of the metabolic defect. The patient with Nieman-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.[29]

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, understandably, 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.

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