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Liver Transplantation for Tyrosinemia:

A Review of 10 Cases from the University of Pittsburgh

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Hereditary tyrosinemia type I (tyrosinosis) is an autosomal recessive disorder of metabolism characterized by a deficiency of fumarylacetoacetate hydrolase, resulting in the accumulation of abnormal metabolites of tyrosine that are toxic to both the liver and the kidney (1-3). Until the advent of liver transplantation, the only available treatment for this disease was dietary avoidance of aromatic amino acids and methionine. Although such therapy results in some symptomatic improvement, in none of the patients so treated is liver disease prevented, and in most, a relentless progression of the liver disease or the appearance of a hepatocellular carcinoma (HCC) results in death within the first decade of life (1-5).

Despite the fact that the National Institutes of Health consensus conference on liver transplantation in 1983 identified tyrosinemia as one of the metabolic diseases of the liver for which transplantation is indicated and can produce a cure (6), there is still considerable confusion among pediatricians and surgeons as to when such patients should be referred for liver transplantation. In an attempt to answer this question, the outcome of 10 patients with tyrosinemia, who underwent orthotopic liver transplantation at the University of Pittsburgh, was reviewed.

CASE REPORTS

Between January 1981 and December 1987, 1357 liver transplants were performed in 1043 patients at the University of Pittsburgh. Of these 1043, 689 were adults and 354 were children. Eleven of these transplants were performed in 10 patients (nine females and one male) with tyrosinemia. Nine were children and one was a 21-year-old adult (Table 1). In each case, the diagnosis of tyrosinemia was based on the presence of characteristic clinical findings and was confirmed by the presence of elevated plasma and urinary tyrosine, phenylalanine, and methionine levels and the presence of increased levels of succinylacetone in the urine. Each subject had a markedly increased alpha-fetoprotein level (range 2700–180,000).

All but one (OT 498) of these 10 patients had been maintained on a tyrosine-, phenylalanine-, and methionine-restricted diet. This single patient was referred for transplantation without a trial of restrictive dietary management because of the presence of advanced liver disease at the

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time of her initial diagnosis. Six of the nine patients tolerated dietary restriction reasonably well but, while on the diet, developed progressive liver disease that necessitated liver transplantation. As can be seen from Table 1, these six patients were referred for liver transplantation at a much older age than was the case for the three children who were not able to tolerate dietary management.

RESULTS

Of the 10 patients studied, seven are currently alive following liver transplantation with follow-ups ranging from 6 months to 6½ years (Table 1). Of the three who died, the first, a 1-month-old infant died as a result of a technical complication experienced during the transplant procedure (OT 991); the second, who had bilateral chronic subdural hematomas prior to transplant surgery, dies as a result of bronchial aspiration six months after successful transplantation (OT 498); the third died of recurrent hepatocellular carcinoma five months after transplantation (OT 454).

Of the seven surviving patients, six have normal liver function. One developed chronic rejection following a brief cessation of immunosuppression during a bout of pneumonitis due to pneumocystis. In Table 2 is shown the performance status of the seven surviving patients and their physical growth relative to the National Center of Health statistic percentiles. The surviving adult patient is working full-time, while the five children with good allograft function are performing well at school and are developing normally. The single child with chronic rejection has experienced a decline in growth.

All seven surviving patients had normal blood urea nitrogen (BUN) and creatinine levels before transplantation and have continued to maintain good posttransplant renal function (mean posttransplant BUN of 18.4 mg ± 4.9 SD and creatinine of 0.68 mg ± 0.36 SD. Comprehensive data demonstrating the resolution of the clinical and metabolic features of tyrosinemia are available in four of the seven surviving patients (OT 206, 288, 356,400) and have been reported previously (7). All successfully transplanted patients have been maintained on an unrestricted diet.

Three patients had clinically evident HCC prior to transplantation, which had been detected preoperatively as a result of frequent ultrasound monitoring (Table 3). An attempted hepatic lobectomy in one of these patients led to acute liver failure (OT 288). This patient had no residual carcinoma in the liver remnant at the time of transplantation and is currently alive 56 months following transplantation without any evidence of residual tumor. A second patient (OT 206) required a second transplant for graft rejection but is nonetheless alive 78 months following initial transplantation without evidence for residual cancer. The third patient (OT 454) had an extensive tumor in the right lobe, which was found to be invading the portal vein and, as a result, was given posttransplant chemotherapy. Despite the chemotherapy, he died of tumor recurrence five months after transplantation. Two additional patients (OT 356, OT 400) had HCC in their hepatectomy specimens that were not detected during their pretransplant evaluations (Table 3). Both are currently alive and well 48 and 42 months following transplantation without any evidence of residual tumor.

All five of the patients found to have HCC were >2 years of age. None of the patients <2 years of age had a HCC. However, all of the cases <2 years of age had cirrhosis and focal areas of hepatocellular dysplasia (small foci of hepatocytes with large hypochromatic nuclei) on histologic examination of their resected livers.

DISCUSSION

Liver transplantation for tyrosinemia was first performed in 1976 (8). Since then, there have been several such reports, each of which consists of a small number of cases (9-11). However, none have been as large as this series and none have addressed the issue of hepatocellular carcinoma and the timing of transplantation.

Tyrosinemia presents in two different forms. In the acute form, symptoms appear within the first few months of life with vomiting, diarrhea, lethargy, hepatosplenomegaly, and failure to thrive. Although some of these patients with an acute onset improve, at least temporarily, with strict dietary restriction, most die within the first year of life of progressive liver failure (1-5). Three of our patients (OT 498, 776, and 991) presented with the acute form of the disease with rapidly progressing liver failure. Two of these three survived the operation. Despite the fact that the incidence of technical complications of liver transplant surgery leading to a transplant mortality are great in children < 1 year of age (12,13), the only opportunity for survival in such acute cases is liver replacement. Survival rates of 50–60% are obtained in this age group with transplantation and clearly justify performance of the procedure for this indication in such small children.

In the chronic form of the disease, patients typically present with rickets and growth retardation. Evidence for liver disease in such cases is present in the form of ascites, jaundice, or a coagulopathy. Few such children reach adulthood, as did one of our patients (OT 288). The majority die during the first decade of life, either as a result of progressive liver disease or the development of a HCC (1-5). Dietary restriction in patients with the chronic form of the disease delays the onset of some of the clinical features of the disease and often allows these children to grow and survive beyond the first year of life. Since HCC does not appear to occur before the age of 2 years in children with tyrosinemia, liver transplantation should be offered to children with tyrosinemia after 1 year of age, when transplant results are improved but before 3 years of age, when HCC is likely. Such an approach to transplantation would maximize transplant survival without the additional problem of HCC.

Seven of our 10 patients present with the chronic form ofthe disease (OT 206, 288, 356, 400, 454, 770, 1107). Six are alive 9–78 months following transplantation. Five have normal liver function; one has chronic rejection (OT 776). The single death in this group occurred as a result of recurrent HCC. This child was transplanted after 2 years of age.

It is very encouraging to observe increased growth following transplantation in all but one of the surviving children. Three of the five children with good allograft function have shown marked increases in their percentile growth compared to their pretransplant levels (Table 2). Not surprisingly, the single adult, and the only child with chronic rejection have not exhibited any posttransplant growth acceleration.

Van Thiel et al (7) and Flatmark et al (11) have demonstrated improvement in the renal tubular dysfunction of patients with tyrosinemia following liver transplantation. All seven surviving patients in this series, as in these two earlier series, have maintained good posttransplant renal function with mean BUN and creatinine levels of 18.4 mg/dl and 0.68 mg/dl, respectively. Tuchman et al (9) and Van Thiel et al (7) have shown that mild metabolic abnormalities persist following liver transplantation and that these originate from extrahepatic tissues (probably the kidney) with residual fumaryl-*O*-acetoacetate deficiency. The clinical significance of this finding is still to be elucidated but appears not to be a clinical problem, at least in the cases in this series, and probably reflects persistence of the tyrosinemia phenotype by the kidney.

The incidence of HCC in tyrosinemia has been reported to be as high as 37% in patients who survive beyond the age of 2 years (5). The five patients with HCC in this series were all beyond

the age of 2 years, the youngest being 33 months when the tumor was found. The association of tyrosinemia and hepatocellular dysplasia as well as hepatocellular carcinoma is of considerable interest. Hepatectomy specimens in nine of our 10 patients revealed histologic hepatocellular dysplasia characterized as foci of hepatocytes with large hyperpigmented nuclei. It was impossible to correlate age and the degree of dysplasia because of variability of dysplasia not only in the same liver specimen but also within a given nodule. The high incidence of HCC in cases with tyrosinemia beyond the age of 2 years and the probable progression of hepatocellular dysplasia to HCC early in the course of this disease after age 2 years but before age 3 years suggests that liver transplantation might be indicated in all cases with the chronic form of the disease and liver insufficiency beyond the age of 2 years.

Frequent alpha-fetoprotein determinations, hepatic ultrasonograms, and liver biopsy are not without risk and have not been routinely helpful in such cases. Alpha-fetoprotein levels can be elevated markedly in patients exhibiting dysplasia without evidence of carcinoma, as seen in four of the present cases. It is difficult to evaluate the clinical significance of nodular lesions found by repeated ultrasound examinations in a liver with cirrhosis. Moreover, there is a considerable sampling error in biopsying small nodular lesions in cirrhotic livers. One of our patients (OT 454) was followed prior to transplantation with periodic ultrasound examinations. Despite such monitoring, at transplantation he was found to have an extensive tumor invading the portal vein. He died five months after transplant with recurrent HCC. When one considers the risk of death from HCC without OLTx after age 2 years and the current results with liver transplantation performed after age 1 year, serious consideration for early referral of patients with tyrosinemia for liver transplantation after 2 years of age appears advisable.

SUMMARY

Results of liver transplantation in 10 patients with tyrosinemia are reviewed. The indications for transplantation were: hepatoma in three, acute liver failure in two, and progressive chronic liver disease in five. One patient died during surgery. Of the remaining nine who survived the operation, one died at six months as a result of bronchial aspiration and aspiration pneumonia, and a second transplanted for hepatoma died five months later with metastases. Seven patients are alive 6 months to 6½ years following transplantation. Of these seven patients, six have normal liver function and a good performance status. One is awaiting retransplantation for chronic rejection. Hepatocellular carcinoma (HCC) was found either preoperatively or incidentally in five patients, all older than 2 years at the time of their transplant. Four of these are alive and well without evidence of tumor with follow-ups between 3½ and 6½. Four of the five patients less than 2 years of age had hepatocellular dysplasia without evidence of carcinoma on histologic examination of the resected liver. This experience suggests that liver transplantation should be considered seriously for children with hereditary tyrosinemia who are more than 2 years of age because beyond that age the incidence of hepatocellular carcinoma (HCC) increases substantially.

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Table 1

CLINICAL AND PATHOLOGICAL FINDINGS IN 10 CASES REVIEWED

OT* No.	Age in years at time of OLTx	Tolerance of dietary management	Indications for transplant	Hepatoma	Dysplasia	Current status
206	2 9/12	good	hepatoma	yes	yes	alive 78 months after first transplant
288	21	good	acute liver failure after resection for hepatoma	yes	yes	alive 56 months
356	3 6/12	good	chronic liver disease, suspected hepatoma	yes	yes	alive 48 months
400	3	good	chronic liver disease	yes	yes	alive 42 months
454	6	good	hepatoma	yes	yes	died 5 months after transplant
498	6/12	no dietary management	progressive liver failure	no	yes	died 6 months after transplant
770	1 5/12	poor	chronic liver disease	no	yes	alive 21 months
776	6/12	good	progressive liver failure	no	yes	alive 21 months
991	1/12	poor	acute liver failure	no	none	died during surgery
1107	1	poor	chronic liver disease	no	yes	alive 9 months

*OT = Orthotopic liver transplantation.

Table 2

PERFORMANCE STATUS OF THE SURVIVING PATIENTS

OT	*Preop height (percentile)*	*Preop weight (percentile)*	*Duration after transplant (months)*	*Height (percentile)*	*Weight (percentile)*	Observations
206	25	75	78	90	90	Attending school normal LFTs*
288	<5	<5	56	<5	<5	Transplanted at age 21, no further growth, working full-time
356	50	10	48	75	90	Attending school, normal LFTs
400	90	50	42	95	50	Attending school, normal LFTs
770	10	<5	21	10	<5	Attending school, slow growth, Normal LFTs
776	10	25	20	<5	<5	Chronic rejection, awaiting retransplantation
1107	<5	<5	9	25	25	Developing normally, normal LFTs

* LFTs = liver function tests.

Table 3

PATHOLOGICAL FINDINGS IN 5 CASES WITH HCC

OT	Age	Pathology	*Survival (months)*
206	2 9/12	Multifocal hepatomas involving both lobes of the liver measuring up to 2 cm in greatest diameter	78
288	21	Large tumor involving most of the right lobe measuring up to 13 cm in greatest diameter; multiple satellite nodules containing tumor	56
356	3 6/12	Multifocal hepatoma in several nodules involving both lobes of the liver, measuring up to 2.5 cm in greatest diameter	48
400	3	Multifocal hepatoma in several nodules involving both lobes measuring up to 2.5 cm in greatest diameter	42
454	6	Large tumor involving 2/3 of the right lobe of the liver measuring up to 11 cm in the larger diameter; multiple satellite nodules containing tumor and invasion of the portal vein and porta hepatis	5