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Liver Transplantation for Hereditary Tyrosinemia: The Quebec Experience

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Summary

Sixteen tyrosinemic patients were evaluated in our institution for a possible liver transplantation. All patients showed biochemical and/or radiological evidence of liver dysfunction. Renal involvement was found to be more abnormal than expected. Seven patients have been transplanted, with two patients receiving a combined liver-kidney transplant. Hepatocarcinoma was detected in two of eight patients in whom the whole liver was examined. Six (37.5%) of the initial 16 patients have died since evaluation, one of the six dying after combined liver-kidney transplantation. Posttransplantation survival was 86%, with normal liver function, normal growth, and no recurrence of neurological crises on a normal diet.

Introduction

Hepatorenal tyrosinemia is a heterogeneous hereditary disorder affecting numerous organ systems, primarily the liver, the kidneys, and the neurological system. Some children have repeated neurological crises, comprising severe paresthesias, paralysis, and automutilation (Mitchell et al., 1990). Renal involvement is described in detail in another article in this issue of the *Journal* (Russo and O'Regan 1990). Liver involvement may present with acute failure in the first few weeks of life, a slowly progressive deterioration of liver function which evolves toward cirrhosis, or repeated bouts of liver decompensations during intercurrent viral infections (Larochelle et al. 1967). The advent of the liver transplantation has offered a hope of cure for these children, and the use of combined liver-kidney transplantation for children with severe renal involvement has even further ameliorated their prognosis.

Since we began evaluating children as candidates for liver transplantation in 1985, we have had the opportunity to examine 16 children with hepatorenal tyrosinemia. The great majority came from Chicoutimi (Quebec) and surrounding areas (where there is an active parents' association) and were either self-referred or referred by one of the authors (J.L.). In the present report, we describe the reasons for referral, the findings at that time, and the outcome of these affected children, concentrating primarily on their hepatic function.

Methods

Sixteen children were evaluated between January 1985 and September 1989 with standard liver-function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transpeptidase (gamma-GT), bilirubin, coagulation studies, fasting bile acids, albumin, alpha fetoprotein (AFP), ultrasound, and abdominal CT scan. Cirrhosis was suspected in the presence of liver heterogeneity on ultrasound or CT scan evaluation with or without the presence of nodules. Portal hypertension was considered to be present on ultrasound examination if (*a*) there was thickening of the omental wall or presence of venous collaterals or esophageal varices or (*b*) if Doppler studies showed hepatopedal flow through the portal vein. Splenomegaly alone was not considered sufficient evidence of portal hypertension.

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Results

Nine females and seven males ranging in age from 8 mo to 16 years 8 mo (mean 4 years 4 mo) were studied. Eight patients were referred for neurological crises with various degrees of liver dysfunction, two for progressive renal failure and six for progressive liver failure with or without the presence of modules on liver imaging. Those children who were not referred for progressive liver disease all had some abnormality(ies) of their liver-function tests. The results of their laboratory values on initial evaluation are shown in table 1. AST was elevated in 10 (63%) of the children, ALT in nine (57%), bilirubin in five (32%), alkaline phosphatase in five (31%), gamma GT in 12 (92%) of the 13 in whom it was measured, fasting bile acids in eight (67%) of 12; two others with normal fasting bile acids had elevated postprandial bile acids. Prothrombin time was prolonged in nine (57%), partial thromboplastin time in five (31%). Five (31%) of the children had decreased albumin levels.

The results of liver imaging, AFP, and long-term outcome are depicted in table 2. AFP was elevated in 15 (93%) of the children, with values ranging from normal to 22,970 ng/ml. There was a tendency for the highest values to be found in the younger (age <5 years) children. Ultrasound and CT examinations revealed an enlarged liver in 10 (63%) of the children and a small liver in two (12.5%) of them. Hepatic architecture was heterogeneous in 12 (75%) of the patients, with the presence of nodules in 10 (63%) of them. In three patients, nodules which had not been visualized on ultrasound were detected on CT scan. Portal hypertension was seen in seven (44%) of the patients, with splenomegaly alone being detected in one other patient.

Eight (50%) of the children had had repeated neurological "crises" characterized by paresthesias, paralysis, automutilation, or severe pain. Six (37%) of the children have died since 1985. Two died while on the transplant waiting list, three died during a severe neurological crisis, and one died 5 d after a liver-kidney transplantation, from primary nonfunction of the liver graft.

Five children underwent a liver transplantation, and two underwent a liver-kidney transplantation. One of the children died post liver-kidney transplantation, for an overall survival rate of 86%. Hepatocarcinoma in situ was discovered on the resected liver in one transplanted child (VF) and in the autopsied liver of another child (JFM) who died during a severe and prolonged paralytic neurological crisis. All six survivors have normal liver-function tests and are thriving on a normal diet. No patient has had a neurological crisis since transplantation, during a follow-up of as long as 4 years.

Table 1

Results of Clinical and Biochemical Data on Initial Evaluation (normal values)

Patient (age)	AST/ALT (<55 IU/liter <25 IU/liter)	Alkaline Phosphatase (0–2 years, <548 IU/liter)	GGT (1–7 years, 16 IU/liter; 8 years to adult, 30 IU/liter	PT/PTT (controls, 10.5–12.5 s/ 28.5–31.1 s)	Albumin (<3.5 mg/ 100 ml)	Bile Acids (<60 μg/ 100 ml)	Bilirubin T/D (T < 1 mg/100 ml)
HT (16 years 8 mo)	26/31	867	19	11.9/30.6	3.8	46.8	.1/0
NC (2 years 10 mo)	116/29	465		29.2/200	2.9		7.3/3.4
RQ (3 years)	88/20	400	116	17.4/44.9	3.2	19.2	.6/.2
CI (8 years 2 mo)	35/20	171		15.2/38.7	3.1	1,079	2.7/1.2
PB (1 year 6 mo).....	131/33	380	73	15.2/37.3	3.5	194	.2/.1
VF (3 years 3 mo).....	69/54	394	307	13/32	3.8	204	.3/0
SG (3 years 6 mo).....	246/115	554	77	16.2/40	2.9	323	5.4/2.6
NR (2 years)	76/52	369	43	16.3/34.5	5.3	10	1.1/.6
SB (7 years 4 mo)	42/12	365	31	15.5/34.4	3.97	349	1/.2
RD (1 year 9 mo)	64/18	160	73	14/33.9	4.2	19	.3/.1
CG (8 mo).....	109/38	941	126	19.2/56	3.5	429	.9/.3
JSV (11 mo)	89/35	269	48	13.4/38.6	4.2		.8/.4
MLR (1 year 11 mo)....	20/11	174	181	12.7/29.5	3.2		.2/0
JFM (8 years 4 mo).....	13/20	348		11.5/40.5	4.2	90	.3/.1
KB (6 years 4 mo).....	47/29	599	40	15.2/36	4.0	126	2.3/.5
KL (1 year 9 mo)	63/26	473	28	12/32.7	3.8		.8/0

Table 2

Liver Imaging, AFP, and Long-Term Outcome

Patient	AFP	Liver Size	Liver Architecture	Liver Nodules	Portal Hypertension	Spleen Size	Outcome
HT.....	7	Normal	Heterogeneous	–	–	Normal	Liver-kidney transplant for neurological crises and renal failure, alive and well 18 mo post transplant
NC.....	13,200	Normal	Heterogeneous	+	+	Increased	Death from liver failure
RQ.....	10,900	Increased	Heterogeneous	+	–	Increased	Alive, parents considering liver transplantation
CI	33.9	Decreased	Heterogeneous	+	+	Increased	Liver transplant, alive and well 4 years post transplant
PB	500	Decreased	Normal	–	–	Normal	Death from primary nonfunction of liver after liver-kidney transplantation
VF	15,500	Increased	Heterogeneous	+	–	Increased	Alive and well 6 mo post liver transplant, hepatocarcinoma in resected liver
SG	440	Increased	Heterogeneous	+	+	Increased	Died awating liver transplantation
NR.....	177	Normal	Normal	–	–	Normal	Alive and well 7 mo post liver transplant for severe neurological crisis
SB	70	Increased	Heterogeneous	–	+	Increased	Alive and well 12 mo post liver transplant
RD.....	5,000	Increased	Normal	–	–	...	On transplant list for severe neurological crises
CG.....	22,970	Increased	Heterogeneous	+	–	Increased	On liver transplant list
JSV	1,400	Increased	Heterogeneous	+	–	Increased	Alive and well 2 years after liver transplant for severe neurological crisis
MLR ...	205	Increased	Heterogeneous	+	+	Increased	Death from liver failure during neurological crisis
JFM	87	Increased	Heterogeneous	+	+	Increased	Death during paralytic neurological crisis
KB	7	Normal	Normal	–	+	Increased	Alive, parents considering transplantation
KL	50	Decreased	Heterogeneous	+	–	Normal	Parents refused transplantations, death from gastrointestinal hemorrhage during neurological crisis

No recurrence of hepatocarcinoma has been found in patient VF, who is now 7 mo post liver transplantation. The seven livers available for examination after resection for liver transplantation all showed micro- and/or macronodular cirrhosis with the presence of numerous regenerating nodules of various sizes. It is surprising that some nodules which were increasing in volume on ultrasound or CT scan were composed of fat.

Discussion

Tyrosinemia can be a rapidly fatal disease: of the 34 patients detected through the provincial neonatal screening program during 1978–86, 15 died prior to 12 mo of age and another eight died before their second birthday, for a 68% mortality (De Braekeleer 1989). It is surprising that evaluation of our 16 patients revealed gamma GT and serum bile acids to be the most frequently abnormal tests. This may represent a component of biochemical cholestasis as part of their liver dysfunction. We have noted that during viral infections PT and PTT may become very abnormal and then return to their baseline values once the infection is over. Similarly, transaminases tend to fluctuate widely during intercurrent infections. In some cases, what begins insidiously as a seemingly benign infection can progress to liver, kidney, and neurological decompensation. In our experience, anesthesia or sedation for procedures, as well as viral infections, are the most consistent triggers of a crisis. We thus do not perform a liver biopsy systematically, as all our patients have evidence of cirrhosis at transplantation or autopsy, despite almost normal liver function.

Liver transplantation in tyrosinemia corrects the liver metabolic abnormalities and appears to prevent further irreversible neurological catastrophes. Between crises, the children with neurological crises may have normal liver function and normal renal function. De-

spite these normal findings, we feel that liver transplantation is indicated to avert both further neurological deterioration and the risk of permanent sequelae, as well as death, during a crisis, as occurred in three of our patients.

One of the major difficulties encountered in patients with tyrosinemia is the decision as to when is the appropriate time to place them on the transplantation list. It is known that these children are at increased risk of developing hepatocarcinoma, and yet an unknown proportion of them may reach adolescence without this complication. Of the eight whole livers which were available for histological examination in the present study, 25% (two) contained nodules of hepatocarcinoma, a frequency which is not far from the 37%–50% reported in the literature for children older than 2 years (Weinberg et al. 1976; Starzl et al. 1985). As has been noted elsewhere (Day et al. 1987), no imaging technique was able to differentiate between regeneration nodules or hepatocarcinoma: nodules were found to be either hypodense, hyperdense, enhancing, or nonenhancing with contrast as described by Day et al. (1987). Both CT scan and ultrasound examinations are recommended in the evaluation of these children, as nodules may only be detected by one technique and not by the other. No relationship between the presence of nodules containing hepatocarcinoma and elevated AFP could be made, as one of the two patients with carcinomatous nodules has only mildly elevated AFP, and others with very high AFP levels had no carcinoma detected. Needle biopsies under ultrasound guidance of suspicious nodules for histological analysis would be difficult, as most patients have several nodules to be biopsied. Furthermore, this procedure is possibly contraindicated because of the possibility of seeding malignant cells.

Children undergoing liver transplantation for reasons other than tyrosinemia have been shown to have a progressive decrease in their glomerular filtration rate (GFR), a decrease which has been attributed to the nephrotoxicity of cyclosporine (McDiarmid et al. 1989). The long-term renal function of these children remains uncertain and is of particular concern for patients with renal disease present prior to liver transplantation (Tuchman et al. 1987). Almost all of our patients were found to have some renal abnormality, as manifested by either enlarged kidneys with or without nephrocalcinosis on ultrasound or CT examination, a Fanconi syndrome, or abnormal GFR. Liver transplantation in hepatorenal tyrosinemia does not fully correct the metabolic abnormalities, as persistent excretion of succinylacetone by the affected kidneys has been demonstrated, although the long-term significance that this finding has for renal function is unknown (Tuchman et al. 1985). In our tyrosinemic patients who have received a liver transplant alone, the already abnormal pretransplantation GFR has further deteriorated with time. We have thus adopted a policy to perform frequent evaluations of the GFR on patients awaiting transplantation and to carry out combined liver-kidney transplantations in patients with GFRs which are persistently <40 ml/min/1.73 m^2. Growth is impaired in children at this level of GFR, which would be expected to deteriorate even further with cyclosporine treatment (Hodson et al. 1983; Leunissen et al. 1989). These combination transplants are well tolerated and may not require tissue cross-matching, as the grafted liver appears to induce some form of tolerance to the transplanted kidney (Margreiter et al. 1988).

Liver transplantation for metabolic diseases has a higher survival rate than it has for other congenital disease such as biliary atresia, as patients are usually better nourished and have not undergone previous hepatic surgery (Esquivel et al. 1988; Van Spronsen et al. 1989). In hepatorenal tyrosinemia with neurological crises, liver transplantation should be performed as soon as technically feasible. Despite the lack of experience on the relationship of nodules to the development of carcinoma, we have adopted the policy that liver transplantation should be performed early in patients in whom imaging studies reveal hepatic nodules. In the remaining few patients, in whom liver imaging shows normal or stable liver function with no nodules and who have no neurological crises, and adequate renal function and growth, close monitoring (1) for radiological signs of either liver deterioration or the development of nodules and (2) of AFP levels are recommended every 3–6 mo to determine the appropriate time for liver transplantation (McMahon 1986, p. 298). Finally, in patients with deteriorating renal function, combined liver-kidney transplantation should be considered.

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