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Pediatric Liver Transplantation Under Therapy With Cyclosporin-A and Steroids

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DURING the period 5/9/81 to 5/9/82, 27 consecutive liver transplantations were performed on 23 pediatric patients. Ages ranged from 7.5 months to 18 years. There were 11 males and 12 females. Four patients were adolescents (12–18 years), 6 patients were school age (5–10 years), and 13 were infants to preschools (7.5 months–4.5 years). Follow-up time ranged from 3.5 months to 15.5 months. Survival stands at 70% (16/23), while 61% (14/23) can be described as in excellent condition.

Orthotopic liver transplantation (OLT) has, since its inception,[1] been a procedure with high mortality and morbidity. Steady improvement in survival statistics have, however, occurred during the 20-year history of the procedure. Improvements in surgical technique, patient selection, and immunosuppression have moved OLT into the realm of practical therapeutics.

Pediatric OLT, while always enjoying slightly better survival statistics than its adult counterpart,[2] has had added morbidity without correlate in the nonpediatric population. The profound effect of high doses of steroids on the child, which leads not only to growth failure but also to Cushingoid changes, has prompted some to question the use of transplantation in children[3] at all.

We report improved survival statistics for pediatric OLT under cyclosporin-A (CyA) and low-dose steroids, as well as preliminary data suggesting normal growth velocity post-transplantation in these patients.

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MATERIALS AND METHODS

Patient Selection

All the patients listed in Table 1 represent 1-year experience with liver transplantation dating from 5/9/81 to 5/9/82. Nineteen patients received 1 graft and while 3 patients had 2 grafts, and 1 patient had a total of 3 grafts.

Biliary atresia with a failed attempt at restoration of bile drainage by portoenterostomy represented the most frequent indication for liver transplantation in children. Following biliary atresia, are a variety of inborn errors of metabolism (alpha-1-antitrypsin [A_1AT] deficiency being by far the most frequent of the inborn errors), biliary hypoplasia, chronic active hepatitis, neonatal hepatitis, secondary biliary cirrhosis, and familial intrahepatic cholestasis.

Patients who were transplanted were initially placed on a transplant candidacy list following an in-hospital medical evaluation. The evaluation was undertaken to (1) verify acceptable pretransplantation anatomy (generally requiring demonstration of a patent extrahepatic portal vein), (2) review the patient's diagnosis (accomplished by a review of medical records, biopsy slides, and occasionally other further testing), and (3) an attempt at gaugeing the medical urgency of transplantation.

Transplantation recipients were chosen from the candidacy list based on the size of the available organ, the blood type of the organ donor, and the type and severity of the liver disease of the recipient. Selection was made independent of HLA typing or patient donor crossmatch data. While size matching was rather strictly adhered to, one of the patients in the series was an ABO mismatch with the donor. Patients who received grafts either suffered from a disease entity whose course is predictably and rapidly downhill (i.e., biliary atresia), had multifocal neoplasia or neoplasia with cirrhosis complicating metabolic liver disease, or had reached end-stage[4,5] with a liver disease whose course is less predictable (i.e., A_1AT deficiency).[6] One patient in the series did not fall into any of the 3 aforementioned categories and received a transplant. That patient was an A_1AT-deficient child who had developed social invalidism[7] from associated hepatogenic cyanosis.[8]

Surgery

Hepatectomy of the donor organ was performed at the hospital of the donor's death. The organ graft was preserved in Collin's solution during transport.[9] The method of transplantation has been described previous-

Table 1. Indications for Liver Transplantation in Children

Disease	Number of Patients	Survivors	Follow-up Time (Months)
Biliary atresia	7	5	3.5 to 15.5
Inborn error (totals)	8	6	5.0 to 14.0
Alpha-1-antitrypsin	4	2	5.0 to 14.0
Wilson's	1	1	11.0
Tyrosinosis with hepatoma	1	1	9.0
GSD-I	1	1	6.0
Sea Blue Histiocytes with hepatoma	1	1	5.0
Biliary hypoplasia	3	1	8.0
CAH	2	1	4.0 to 5.0
Secondary biliary cirrhosis	1	0	
Neonatal hepatitis	1	1	9.0
Familial intrahepatic cholestasis	1	1	13.0

ly.[10] Cold ischemia time depended to a large extent on the distance to the donor hospital, but in all instances was less than 12 hr. Prophylactic antibiotics were initiated at the time of surgery and continued for 4 days. Further antibiotic use was dependent on the patient's clinical course.

Immune Suppression

The immunosuppressive regimen used has recently been described in detail.[11] Essentially, it consisted of oral CyA initiated 4–6 hr before surgery, or its IV equivalent if 4 hr lead time was not possible, and steroids begun intraoperatively and tapered over the following 5 days from a high dose to a low dose (5–10 mg prednisone) level. Both CyA and steroid therapy were individualized from patient to patient dependent on the patient's clinical status and/or the intervention of rejection episodes. Rejection episodes were treated with bolus of IV Solucortef and/or CyA dosing changes, and/or reinstitution of 5-day prednisone bursts, which begin with high doses of steroids and taper over 4 days to low dose of steroids.

RESULTS

Table 2 lists the follow-up data for the transplanted patients. Sex and age did not affect outcome. Though historically, patients with biliary atresia have had poorer outcome than pediatric patients transplanted for other reasons, disease did not impact on outcome in this series. Finally, clinical condition (defined as grave in hospital-bound patients, fair in those patients living at home under medical management of liver decompensation, and good in patients living at home without any liver decompensation) did not impact on postoperative survival.

Four of the patients had preexisting cytotoxic antibodies to the donor. Table 3 reviews these patients. Antibodies were either ABO isoagglutinins or T-warm cytotoxic antibodies. The latter antibody kills all of the donor lymphocytes in vitro. Though the numbers are small, the data support a real increased risk in these patients. However, it can also be seen from the case material that violating the immunologic barrier presented by preexisting antibodies does not preclude the possiblity of excellent outcome.

Follow-up

Seventy percent (16/23 of the transplanted patients) are survivors, while 61% (14/23 patients) are in excellent condition. Two patients (OT 214, 229) are suffering from chronic rejection.

Figure 1 is the growth curve on one of the transplanted patients. It can be seen that growth velocity following transplantation has been normal in this patient. This patient's growth curve is representative of other patients also transplanted under CyA and low-dose steroids[12] who have 1-year follow-up time.

Five of the patients in this series have follow-ups greater than 1 year. Two of the 5

Table 2. Outcome of 23 Consecutive Pediatric Liver Transplantations

Patient OT No.	Age at Initial Transplant (Years)	Sex	Diagnosis	Condition at Time of Transplant	Present Status	Follow-up Time (Months)	Immune Suppression		
								CyA	
							mg Pred/day	mg/kg/day	Bilirubin
189	2 2/3	M	Biliary atresia s/p Kasai	Good	Excellent	15.5	5	9	< 1
190	4	F	Biliary atresia s/p Kasai	Fair	Excellent	15	5	15	< 1
191	2 1/6	M	Biliary atresia s/p Kasai	Good	Excellent	15	5	10	< 1
192	10 1/2	M	A_1AT	Critical	Excellent, persistent hypertension	14.5	5	9	< 1
193	10 1/6	F	Familial cholestasis	Fair	Excellent	14	5	9	< 1
201	4 1/2	M	A_1AT	Fair	Died with biliary leak and abscess	1 month until death			
202	10 1/2	M	Wilson's disease	Critical	Excellent	11	5	9	< 1
203	18	M	A_1AT with hepatogenic cyanosis	Fair	Died with cerebral hemorrhage after second transplant	3 months until death			
205	2/3	F	Neonatal hepatitis	Critical	Excellent	9	5	16.5	< 1
206	2 2/3	F	Tyrosinemia with hepatoma	Good	Excellent	9	5	16	< 1
213	2	M	Biliary atresia s/p Kasai	Good	Excellent	8	5	9	< 1
214	2 2/3	M	Biliary hypoplasia	Critical	Fair, ongoing chronic rejection	8	10	16	17
216	1 5/6	F	Biliary atresia s/p Kasai	Good	Died 2° to liver failure of rejection	3 months until death			
218	17	F	GSD I with adenomata	Good	Excellent	7	10	12.5	< 1
220	8 2/3	F	Choledochal cyst 2° biliary cirrhosis	Critical	Died at 2nd attempt at grafting, failed 2° portal vein obstruction				
222	7	F	Sea-Blue histiocytosis	Good	Excellent	6	15	12	< 1
226	3	F	A_1AT	Critical	Excellent	3 1/2	5	12	< 1
228	3 1/3	M	Biliary hypoplasia	Fair	Died 2° to sepsis	1/2 month until death			
229	16	M	Chronic active hepatitis	Critical	Critical with chronic rejection	3 1/2	30	30	19
232	6 2/3	F	Biliary atresia	Good	Died with ischemic liver injury	1/3 month until death			
233	1 2/3	F	Biliary hypoplasia	Good	Died at surgery, found to have SVC absence	Immediate postoperative death	5	12	< 1
236	3	F	Biliary atresia s/p Kasai	Fair	Excellent	3	10	17	< 1
237	16	M	Chronic active hepatitis	Critical	Excellent	3	20	20	< 1

patients were school age and 3 were preschoolers. Only 1 patient had significantly delayed development (OT 189) at the time of transplantation. That patient had required monthly hospitalizations for GI bleeding and fluid and electrolyte imbalance from age 1.5 years until transplantation at age 4 years. The remaining toddlers were transplanted early enough in the course of their diseases that severe morbidity had not occurred, while the school-age children had only had decompensated disease in the months prior to transplantation.

Table 3. Outcome of Patients With Preexisting Cytotoxic Antibodies

Patient	Antibody	Outcome
OT 190	T warm	Mild persistent rejection, controlled after 3 months of weekly steroid bolus therapy
OT 193	ABO isoagglutinin	Excellent
OT 229	T warm	Chronic rejection, will require retransplantation
OT 232	T warm	Died with massive liver ischemia without apparent vascular obstruction

Follow-up developmental and psychometric testing has revealed normal developmental progression in the 4 pretransplantation "normal" children and developmental catch-up, though still delayed for age, in the pretransplantation delayed child.

Complications

Hypertension was the most frequent postoperative complication encountered. It occurred to some degree in all but two of the patients. The hypertension generally resolved after 2–3 months. There have been two

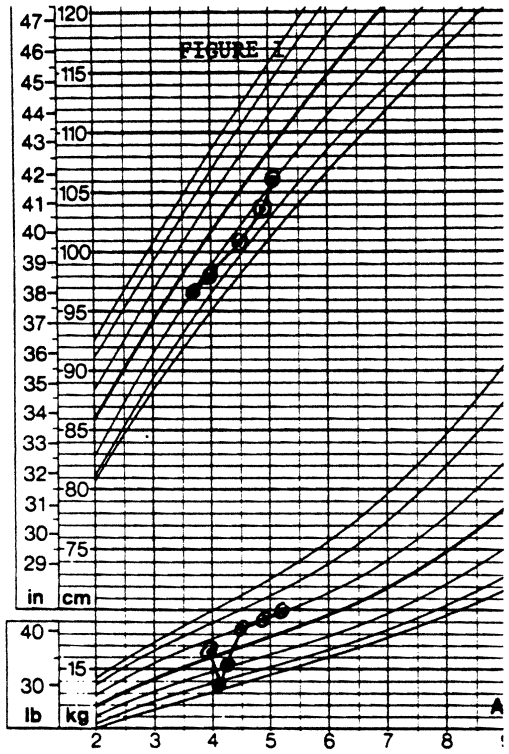

Fig. 1. Patient growth curve.

patients who were exceptions to this. Patient OT 192 has had late recurrence of hypertension, and patient OT 206 has had persistence of postoperative hypertension.

Pulmonary edema in the immediate postoperative period occurred with some frequency early in the series. More conservative fluid management in the patients transplanted in the latter half of the series has decreased this problem considerably.

Renal dysfunction with low fractional urinary sodium excretion occurred in a number of patients and was either hepatorenal or CyA induced. Normalization of renal function occurred either with time and a good functioning graft or with decreases of CyA dosing. Two patients required a short period of discontinuation of CyA with a switch to azothiaprine until renal function recovered (2 days). Reinstitution of CyA at a lower dose did not cause recurrence of renal dysfunction.

Postoperative fever occurred in 18/23 patients. Etiology was viral infection in 2 cases (EBV in 1 patient and CMV in another), bacterial infection in 4 cases (cholangitis in 1 patient, peritonitis in 1 patient, phlebitis in 1 patient, and biliary abscess in 1 patient), fungal in 1 case (candida liver abscess), and nocardia in 1 case (pulmonary nocardosis). Of the remaining 10 patients, fever was associated with biopsy proven rejection in 4 patients and presumed rejection in 2 patients. Of the 4 patients with unexplained fever, one later developed rejection, while in 3 patients fever resolved without explanation. Two of the patients in the series (OT 213 and 229) had infection and rejection. The former had CMV and mild rejection, while the latter had pulmonary nocardosis and severe rejection.

A number of single complications, including recurrent laryngeal nerve injury, phrenic nerve injury on the right, obstruction of the portal vein at the anastomosis site requiring reoperation and correction, and peroneal palsy with foot drop, occurred.

Deaths in the series were clearly rejection-mediated in only 1 patient. One patient had sudden liver failure with marked transaminase rise at 1 week posttransplantation. Postmortem evaluation revealed an ischemic liver despite patent vascular anastomoses. One patient thought to have a patent portal vein by preoperative sonography had a completely thrombosed portal vein at the time of surgery and hence was unable to receive a surgically acceptable transplant. Another patient had an absent superior vena cava (SVC) with upper body venous drainage ultimately returning to the heart by way of the inferior vena cava (IVC). That patient died intraoperatively at the time of cross clamping of the IVC. One patient had a biliary abscess that led to his demise, while another patient died due to overwhelming sepsis. Finally, one patient died following a third attempt at transplantation due to an intracranial hemorrhage.

DISCUSSION

Review of the patient data has shed light on a number of points. Two presuppositions: (1)

that patients with biliary atresia have a poorer outcome at liver transplantation versus children with other indications for liver transplantation owing to the greater difficulty of surgery in the child with previous abdomenal surgery (i.e., portoenterostomy), and (2) that the more gravely ill patients do less well than the more stable patients, did not hold true. Failure of these presuppositions to hold in this series may be merely a function of its small numbers, but, alternatively, it may be due to the coming of age of the actual surgical procedure of liver transplantation, while the immunologic barrier remains the major problem to be surmounted. The rapid normalization of severe metabolic derangements following successful transplantation have allowed the sickest of patients (OT 202, 237) to come back from the brink of death, while other patients (OT 216, 232) in stable condition at the time of transplantation have gone on to their demise following rejection or apparent rejection of the transplanted organ.

The patient data to date support the use of OLT in pediatric patients. Essentially since its inception, the use of OLT in children has been controversial. Starzl et al. have felt that children are excellent liver transplantation recipients, and point to their better survival statistics compared to adults. Calne et al. have been reluctant to perform transplantation in the pediatric age group for several reasons, the foremost being the known long-term toxic side effects of immunosuppressive drugs, especially corticosteroids which causes growth retardation and associated Cushingoid features.

The description by Borel et al.[13] of a fungus extract, CyA, which is a powerful immunosuppressant and which was later shown to be an effective antirejection agent, either by itself[14] or in conjunction with low-dose steroids,[11] held the promise of eliminating the major toxic side effects of previous immunosuppressive regimens. Our data to date support the value of CyA in reducing the toxic side effects of previous immunosuppressive therapy. Children on the regimen of low-dose steroids and CyA not only show improved survival but attain normalization of growth velocity posttransplantation. Whether other delayed or more subtle toxic effects of CyA and low-dose steroids in children will later occur will have to await longer follow-up time.

ADDENDUM

Since submitting this article five more months of follow-up time have passed. The two patients suffering from chronic rejection (OT 214, 229) have succumbed to complications of their rejection or therapeutic intervention taken in an attempt to control rejection. The remaining 14 patients are continuing to do well.

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