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Liver Transplantation for Extra Hepatic Biliary Atresia

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NAGRAL, S., MUIESAN, P., VILCA-MELENDEZ, H., MIELI-VERGANI, G., BAKER, A., KARANI, J., HOWARD, E., RELA, M. and HEATON, N. *Liver Transplantation for Extra Hepatic Biliary Atresia.* Tohoku J. Exp. Med., 1997, **181** (1), 117-127 —— Kasai portoenterostomy has transformed the prognosis for children with Extra Hepatic Biliary Atresia (EHBA). However, for children developing end stage liver disease following portoenterostomy, liver transplantation (OLT) is the treatment of choice. Between February 1989 and March 1996, 64 children with EHBA underwent 79 transplants (26 males, 38 females; median age 2.2 years, range 5 months-17 years; median weight 11.4 kg, range 5-65 kg). Of these, 58 (85%) had undergone previous portoenterostomy. Nineteen patients (30%) had gastrointestinal bleeding prior to OLT assessment. Mean serum bilirubin was 229 μmol/liter (range 11-801 μml/liter). Four children had associated polysplenia syndrome. Of the 79 transplants, 30 received whole and 41 reduced-size cadaveric grafts and 9 living related grafts. Eleven patients (17%) died, nine within one month of surgery. Thirteen patients were retransplanted once and one twice. There were 16 vascular complications (10 hepatic artery thrombosis, 3 portal vein thrombosis, 3 venous outflow obstruction) and 10 biliary complications (4 anastomotic leaks, 6 strictures). Ten patients (16%) had bowel perforation following the transplant. The 5 year actuarial patient and graft survival for this group is 84% and 69% respectively with normal physical and mental development in the majority. OLT provides satisfactory treatment for children with EHBA with end stage liver disease with long term survival in the majority. ———— biliary atresia; liver transplantation; portoenterostomy

Extra Hepatic Biliary Atresia (EHBA) was regarded as a fatal disease until the introduction of the Kasai portoenterostomy which transformed the outlook for

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many of these children. Long term survival is now well documented and actuarial survival rates of approximately 60% at five years without transplantation have reported from centres with a large experience and a special interest in the management of the disease (Howard 1991). Although the Kasai procedure has enabled long term survival in a significant number, some children fail to drain bile adequately or in the longer term develop complications of chronic liver disease.

The development of liver transplantation (OLT) as a viable treatment for end stage liver disease has allowed further improvement in survival for children with biliary atresia. A consensus has emerged that Kasai portoenterostomy should be the first line treatment for EHBA and that OLT should be reserved for those who do not respond to the Kasai procedure (Otte et al. 1994). EHBA constitutes 40% of the paediatric OLT's performed for chronic liver disease at our centre and remains the commonest indication. We report our experience of liver transplantation for EHBA.

Methods

The data was collected from our surgical database and medical notes. Between February 1989 and March 1996, 205 paediatric liver transplants were performed at our centre. During this period 64 children with EHBA underwent 79 liver transplants. There were 26 males and 38 females, median age 2.2 years (range 5 months-17 years), median weight 11.4 kg (range 5–65 kg). Twelve children were less than one year old. Ten children were ten years or older. Fifty-eight patients (85%) had previously undergone Kasai portoenterostomy. Operative procedures undergone by the group prior to OLT are detailed in Table 1.

Nineteen patients (30%) had gastrointestinal bleeding prior to OLT assessment. Of these, 13 had undergone at least one session of sclerotherapy. The mean serum bilirubin at transplantation was 229 μmol/liter (range 11–801 μmal/liter). The mean serum albumin was 34 g/liter (range 23–50 g/liter). Thirteen children had associated congenital anomalies and these are summarised in Table 2.

Of 12 children transplanted under 1 year of age 8 never cleared their jaundice after the Kasai procedure. Two presented with acute liver decompensation after

Table 1. *Previous operative procedures*

	Number
Kasai portoenterostomy	58
Revision of Kasai portoenterostomy	4
Lieno-renal portosystemic shunt	3
Enterostomy	2
Portocholecystostomy	2
Cholecystoenterostomy	1

TABLE 2. *Associated congenital anomalies*

Anomaly	Number
Hypoplastic portal vein	9
Polysplenia, absent IVC, malrotation	2
Polysplenia, absent IVC, malrotation, preduodenal portal vein	1
Polysplenia, situs inversus, preduodenal portal vein	1

IVC, Inferior Vena Cava.

a stable period and have been described in a previous report (Corbally et al. 1994). The other two had not undergone a portoenterostomy. The main clinical features of those children older than one year at the time of transplantation are shown in Table 3.

Overall 9 children were jaundice free at transplantation. The indications for OLT in this group included recurrent encephalopathy associated with poor school performance in 2, severe portal hypertension in 2, recurrent cholangitis in 1, acute liver failure in 1, hepato-pulmonary syndrome in 1 and low diastolic hepatic artery flow in 1.

The procedures of organ procurement and transplantation were performed as per standard techniques described (Corbally et al. 1995; Rela et al. 1995a). The details of liver reduction techniques have been described previously (Heaton et al. 1995). Venovenous bypass was not used. A donor iliac arterial conduit anastomosed to the infrarenal aorta was used to re-arterialize recipient with small native arteries, if there were multiple donor arteries and in children undergoing retransplantation. The arterial anastomosis was performed using a triangulation technique with interrupted sutures (Rela et al. 1995b). Biliary reconstruction was performed with a Roux-en-Y hepatico-jejunostomy. The average length of the Roux loop was 45 cm. Those children with a pre-existing surgical porto-systemic shunt underwent shunt ligation at the time of transplantation. Living

TABLE 3. *Clinical features at primary transplantation in children over one year (n = 52)*

	Number	(%)
Jaundice (bilirubin > 20 μmol/liter)	44	(88)
Cholangitis	18	(36)
Ascites	30	(60)
Variceal bleed	19	(38)
Growth retardation/failure to thrive	14	(28)
Encephalopathy	3	(6)
Severe bone disease	3	(6)
Hepato-pulmonary syndrome	2	(4)

related transplantation was performed within a set protocol of informed consent and thorough pretransplant donor evaluation.

Primary immunosuppression was with cyclosporin, azathioprine and steroids. Six children received cyclosporin in the form of Neoral (Sandoz, Basel, Switzerland) as part of a trial. FK506 was used for rescue therapy in patients with acute rejection not responding to pulse steroids or developing features of chronic rejection. The children were monitored in the postoperative period with regular Doppler ultrasound examinations for vessel patency. If ultrasonic or clinical doubt existed concerning the vascular inflow a selective hepatic angiogram was performed.

Statistical Analysis. Survival was calculated with life table analysis and survivals were compared with Cox regression analysis. Categoric variables were compared with Fishers exact test or Yates corrected chi square test as appropriate. A p value of <0.05 was considered significant.

Results

There were 64 primary and 15 retransplants (one child was retransplanted twice). The mean time on the waiting list prior to transplantation was 2.3 months. The average interval between the Kasai portoenterostomy and liver transplantation was 47 months (range 3–204 months). At the time of first transplant 49 children were at home, 14 were in hospital and one on the intensive care unit.

The mean operative time was 6.4 hr (range 4.5–10 hr) with a median blood loss of 1480 ml (range 200 ml–17 liter). For retransplantation the corresponding figures were 8 hr (range 7–11 hr) and 2,425 ml (range 500 ml–6 liter). There were no intraoperative deaths.

In the primary transplant group 23 patients received a whole and 41 a reduced-size graft, including 5 as part of a split liver procedure and 8 living related liver transplants (LRLT). Of the 41 who received reduced sized grafts there were 6 right and 12 left lobes and 23 left lateral segments (including 8 LRLT).

In the retransplant group 7 patients received a whole and 8 a reduced sized liver (3 left and 2 right lobes and 3 left lateral segments including one LRLT and one split liver graft). Hepatic artery reconstruction was performed using the native artery in 31 and an infra-renal donor iliac artery conduit in 33 of the primary transplants. Arterial reconstruction was achieved in the retransplant group using a conduit in 14 cases (by utilising a previous conduit in 11 and constructing a new one in 3). Of 61 patients with a previous Kasai portoenterostomy the previous Roux loop was used in 58 cases whilst a new one was created in 3.

TABLE 4. *Comparison between early and later parts of the program (primary transplants)*

	Pre July 1993 ($n=21$)	Post July 1993 ($n=43$)	p Value
Reduced Graft	4 (20%)	34 (85%)	<0.001
Conduit	5 (25%)	28 (66%)	<0.005
HAT	5 (22%)	6 (14%)	0.48
Retransplant	6 (30%)	9 (17%)	0.53
Mortality	8 (40%)	3 (7%)	<0.001
2 year actuarial survival	68%	95%	0.003

n = number of patients.

Survival

The mean follow up of the group is 20.3 months (range 2-89 months). The 5 year actuarial patient and graft survival for the whole group is 83% and 69% respectively. When the group was split into pre- and post-July 1993 (Table 4) to compare the early and later parts of the program, the actuarial patient survival at two years was 65% and 93% for the two periods, respectively ($p=0.003$). The rate of retransplantation was 23%. Overall, 9 patients (11%) died within a month of primary transplantation or retransplantation. Of these, 5 died following retransplantation, performed for hepatic artery thrombosis (HAT) in 3 and venous outflow obstruction in 2. One child with HAT developed cerebral lymphoproliferative disease after retransplantation. Other deaths were due to portal vein thrombosis in one, severe graft dysfunction in one, intra-abdominal bleeding in one and venous outflow obstruction and intracerebral haemorrhage in one. One child died six weeks following OLT due to graft dysfunction, bile duct necrosis and septicemia and another child developed chronic rejection, sepsis and died awaiting retransplantation at one year. Seven of the nine early postoperative deaths occurred in the first 4 years of the program.

Complications

Retransplantation

Thirteen patients were retransplanted once and one patient twice. The indications for retransplantation included HAT in 8, venous outflow obstruction in 2, chronic rejection in 3, graft dysfunction of obscure etiology in one and recurrent cholangitis due to impaired biliary drainage in one. The child who was retransplanted twice for chronic rejection has developed recurrent chronic rejection and is awaiting retransplantation.

Vascular complications

Arterial. Ten patients with primary transplants (16%) developed hepatic artery thrombosis (7 whole and 4 reduced sized grafts). Of these, 7 were retransplanted and 3 died. One patient died before being retransplanted. There were thus four deaths attributable to HAT. One patient has developed good collaterals and has normal liver function with a mild intrahepatic cholangiopathy on percutaneous transhepatic cholangiography. Another patient had early recanalisation of the hepatic artery and has no evidence of graft dysfunction.

Portal. Three patients developed portal vein thrombosis one of whom died before being retransplanted. One child was re-explored and portal vein thrombectomy and reanastomosis was performed successfully, in the third child the portal vein recanalised spontaneously. One patient developed portal vein stenosis and portal hypertension following LRLT and has been managed with injection sclerotherapy.

Venous outflow. Three children developed venous outflow obstruction and presented in the immediate postoperative period with impaired graft function. One was retransplanted, but died with multiorgan failure. One child who had graft dysfunction secondary to venous outflow obstruction died of cerebral haemorrhage before being retransplanted. The other child retransplanted as an emergency for HAT died at 20 days with symptomatic venous outflow obstruction.

Biliary complications

Four children had biliary anastomotic leaks and underwent surgical repair. One child died after operative repair of an anastomotic leak from graft dysfunction and sepsis. One leak was secondary to HAT and although it was surgically repaired, the child went on to develop intrahepatic biliary strictures and was retransplanted. Of the other two children, one went on to develop an anastomotic stricture which was successfully managed by percutaneous transhepatic balloon dilatation.

Six children developed biliary strictures. Of 3 with anastomotic strictures, 2 underwent surgical revision and one responded to percutaneous transhepatic balloon dilatation. Of 3 patients with intrahepatic strictures two were associated with hepatic artery thrombosis. One of these patients died after retransplantation whilst the other developed good collateralisation around the arterial thrombosis and responded to conservative therapy. The third patient was managed conservatively and has normal liver function.

One child with polysplenia syndrome which included an absent inferior vena cava was transplanted with a left lateral segment. The left hepatic vein of the graft was anastomosed to the common opening of the recipient hepatic veins end to end and resulted in graft rotation. This led to non-dependent biliary drainage, intermittent biliary stasis and cholangitis and the child was retransplanted.

Infections

Five patients developed pneumonia in the postoperative period including one with Pneumocystis Carinii and another with Cytomegalovirus (CMV). Four patients had evidence of CMV infection including hepatitis in 2. Other significant infections included toxoplasmosis in one child and cervical tuberculosis in another.

Rejection

Overall there were 51 episodes of acute rejection in 34 patients. Twelve children were converted from cyclosporin based therapy to Tacrolimus based therapy. Four patients developed chronic rejection and all were retransplanted. One child had 2 retransplants for chronic rejection and has again developed chronic rejection and is awaiting retransplantation.

Lymphoproliferative disease (LPD)

One child has developed an abdominal Non-Hodgkins lymphoma 4 years following retransplantation for chronic rejection. Another child died following cerebral lymphoproliferative disease following retransplantation for HAT. Both patients had received Tacrolimus based immunosuppression and had evidence of Epstein-Barr virus related LPD. One of these children had undergone splenectomy and lieno-renal shunt 6 weeks before the transplant.

Other complications

There were 12 episodes of bowel perforation in 10 patients. Of these, 8 were in the small bowel (including 2 in the Roux loop), 2 in the large bowel and 2 in the duodenum. Three children had more than one perforation. All patients had undergone at least one abdominal operation prior to OLT and two had undergone 2 previous laparotomies. All perforations were treated surgically with no long term sequelae. Two patients reperforated and a short segment of small bowel was resected at the subsequent laparotomy.

Other significant complications included postoperative bleeding in one child, intra-abdominal collections in 5 patients, 4 of whom were treated by ultrasound guided evacuation and diaphragmatic palsy requiring diaphragmatic plication in two patients.

Discussion

Patients with EHBA pose some specific problems for liver transplantation. Previous surgical procedures make the transplant more difficult and predispose to a higher incidence of bowel perforation after transplantation as seen in 16% of children in this series. This is similar to the incidence of bowel perforation in other reported series (Wood et al. 1990).

This is probably related to difficult dissection of adhesions and the use of diathermy, but other factors such as portal hypertension, high dose steroids and herpes simplex infection may contribute (Shaked at al. 1993). Of 13 paediatric patients with bowel perforation following OLT in our overall series of 215, 10 were transplanted for EHBA. All these patients had undergone a previous Kasai portoenterostomy. Despite the increase in complications previous portoenterostomy does not significantly alter the long term outcome following transplantation (Kalayoglu et al. 1993) and in our series bowel perforation was not a cause of mortality.

The presence of associated congenital anomalies especially those constituting the polysplenia syndrome can also complicate the transplant procedure. Although early reports questioned the advisability of OLT in this subgroup of patients later experience has shown that the vascular anomalies can be technically surmounted (Lilly and Starzl 1974; Hoffman et al. 1989). Four patients (6%) in our series had multiple vascular anomalies related to the polysplenia syndrome. One of these patients underwent a retransplant for recurrent cholangitis due to non-dependent biliary drainage resulting a rotated left lateral segment graft as already mentioned and was successfully retransplanted. In cases with an absent inferior vena cava the donor suprahepatic cava was anastomosed to the common channel of the recipient hepatic veins at a level just below the diaphragm. A preduodenal portal vein or situs inversus did not pose any particular problem for vascular anastomosis. All four patients with the polysplenia anomaly are at present doing well with good graft function. Eleven patients had isolated portal vein hypoplasia and in these cases the portal vein was dissected proximally towards the spleno-mesenteric junction or fishmouthed. In these patients the anterior layer of the portal vein anastomosis was usually performed with interrupted 6/0 or 7/0 polypropylene sutures. None of the children with portal vein anomaly developed portal vein related complications. Our overall incidence of portal vein thrombosis was 3 of 215 paediatric transplants.

The majority of transplants in this series (62%) were performed using reduced sized adult grafts. This is the same as for indications other than biliary atresia (61%) and the use of reduced grafts is increasing (Table 4). Although this increase is due in part to the shortage of size matched paediatric organs it also reflects our ability to utilise adult livers by performing liver reduction or increasingly split liver transplantation. Although the liver reduction may increase the cold ischemia time and intraoperative blood loss due to bleeding from the cut surface, there does not appear to increased mortality, however, morbidity may be higher (Kalayoglu et al. 1993). Five children received a left lateral segment as a part of a split liver procedure and we believe that this represents a way forward for improved utilisation of young donor liver grafts (De-Ville-de-Goyet 1995).

The overall incidence of HAT in this group was 16% and it was the commonest indication for retransplantation (8 out of 15 retransplants), as well as

contributing to 4 of the 9 immediate postoperative deaths (44%). We have shown that the incidence of arterial complications following revascularisation with an infra-renal donor iliac conduit is lower than with the native artery and that a combination of arterial conduit and a reduced sized adult liver has the lowest incidence of arterial thrombosis (Rela et al. 1996). The use of iliac artery conduits for arterial reconstruction has increased significantly over the last 3 years and may account for the decrease in the incidence of HAT (Table 4).

Three patients receiving a reduced sized graft developed hepatic venous outflow obstruction and our method of left hepatic vein anastomosis has changed to that of the triangulation technique (Emond et al. 1993) and subsequently this complication has not been observed. The majority of retransplants and early postoperative deaths were consequent upon technical problems and occurred in the first half of the program indicating a learning phase (Table 4). A comparison of cumulative 2 year survival in the pre and post 1993 shows a significant improvement in the latter half and emphasizes the early learning curve for paediatric liver transplantation (Table 4).

Living related liver transplantation has emerged as an alternative technique of transplanting children. The results of LRLT in our small series showed an 88% patient and graft survival at a median follow up of 21 months and compares with that reported by others (Tanaka et al. 1994).

The majority of children in this series were transplanted after Kasai portoenterostomy. Our institutional policy is to treat all patients with Kasai portoenterostomy unless they present very late. The role of liver transplantation as primary therapy in EHBA has been controversial and although there are proponents of this approach (Gellis 1984) the evidence up to now indicates that this should be reserved for children presenting beyond 120 days of age with an enlarged and hard liver (Kasai et al. 1989). Primary OLT was performed in this series in 4 children. Overall the mean age at which the Kasai procedure was performed was 8.5 weeks.

The need for transplantation following a portoenterostomy is dictated by the technical expertise of the surgeon performing the procedure, the timing of surgery and selective reoperation in a small group of patients who subsequently fail to excrete bile. A recent report of 10 year survival of 74% in children undergoing portoenterostomy before 60 days attributed this success to these factors (Kasai et al. 1989).

The clinical features of children transplanted after one year of age included persistent jaundice, recurrent cholangitis, failure to thrive, ascites and variceal bleeding. Although the mean age at OLT was 4.2 years, 11 children were aged between 5–9 years and 10 over 10 years of age reflecting the success of portoenterostomy in prolonging survival without the need for early transplantation. Children are able to grow to an age and size where the possibility of getting an appropriate size matched graft for OLT is higher (Wood et al. 1990).

This series included 2 children with acute liver decompensation secondary to liver necrosis superimposed on the biliary cirrhosis. Both were well with compensated liver disease prior to presentation with a febrile illness and acute liver decompensation. Both underwent emergency transplantation and survive with good graft function. Children with this clinical picture of high serum transaminases, prolongation of the international normalised ratio and progressive hepatic coma should be listed urgently for transplantation (Corbally et al. 1994).

The five year patient and graft actuarial survival of 83% and 69% respectively seen in this series compare with other series that have been reported (Vacanti et al. 1990; Kalayoglu et al. 1993). A majority of the transplanted children have normal physical and mental development and attend school.

Liver transplantation has proved an effective treatment for children with EHBA and end stage liver disease and the results have improved with time due to technical and medical advances. The emphasis on early diagnosis, referral and portoenterostomy must continue and is particularly relevant to countries without liver transplant programmes. There is a need for identifying the patients who are not going to respond to portoenterostomy so that they can be referred early for transplantation (Wood et al. 1990).

Transplantation and portoenterostomy should be viewed as complementary rather than competitive procedures in the management of children with extrahepatic biliary atresia (Otte et al 1994). A well structured program of multidisciplinary management is essential if long term survival of these children is to continue to improve.

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