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Liver transplantation for arteriohepatic dysplasia (Alagille's syndrome)

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Abstract. Thirteen out of 268 children (< 18 years old) underwent hepatic transplantation (OLT) for end-stage liver disease (ESLD) associated with arteriohepatic dysplasia (AHD). Seven children are alive and well with normal liver function. Six children died, four within 11 days of the operation and the other two at 4 and 10 months after the OLT. Vascular complications with associated septicemia were responsible for the deaths of three children. Two died of heart failure and circulatory collapse, secondary to pulmonary hypertension and congenital heart disease. The remaining patient died of overwhelming sepsis not associated with technical complications. Seven patients had a portoenterostomy or portocholecystostomy early in life; five of these died after the OLT. Severe cardiovascular abnormalities in some of our patients suggest that complete hemodynamic monitoring with invasive studies should be performed in all patients with AHD, especially in cases of documented hypertrophy of the right ventricle. The improved quality of life in our surviving patients confirms the validity of OLT as a treatment of choice in cases of ESLD due to AHD.

Key words: Alagille's syndrome, liver transplantation – Liver transplantation, Alagille's syndrome – Arteriohepatic dysplasia (Alagille's syndrome), liver transplantation

Arteriohepatic dysplasia (AHD) is a dominant, autosomic disorder characterized by intrahepatic cholestasis and peripheral pulmonary artery stenosis. Patients frequently have abnormal faces, vertebral anomalies, posterior ocular embryotoxon, and growth retardation [2, 3, 9, 14]. This syndrome is histologically defined as a significantly decreased ratio of the number of interlobular bile ducts to the number of portal areas (< 0.4). In fact, "paucity of interlobular bile ducts" is presently the generally accepted definition [3]. The progression of the liver disease is variable. Alagille reported that 88% of the patients maintained normal hepatic function while 12% developed cirrhosis [1]. Management of these children is usually entirely medical. However, patients with severe cholestasis, malnutrition, and progressive portal fibrosis should undergo orthotopic liver transplantation (OLT). The course of 13 AHD children who had OLT in our institution is reported.

Patients and methods

In the period from March 1980 to September 1986, 268 children underwent OLT at the Children's Hospital of Pittsburgh (Fig. 1). All patients were treated with cyclosporin and prednisone [11]. Of these patients, 13 (10 male and 3 female) had advanced liver disease secondary to AHD. The diagnosis was based on liver histology, showing paucity of interlobular bile ductules, and the presence of peripheral pulmonary artery stenosis, based on clinical data or findings at autopsy. Surgical investigation of cholestasis had been performed in all 13 patients in the first 2 months of life. Before transplantation, all patients were evaluated with electrocardiograms and echocardiograms and were seen by pediatric cardiologists who cleared them for surgery. One patient with severe pulmonary ventricular outflow obstruction, detected by an echocardiogram, had a cardiac catheterization before OLT. Dilatation of the pulmonary valvular stenosis was performed. A repeat cardiac catheterization, performed a few days

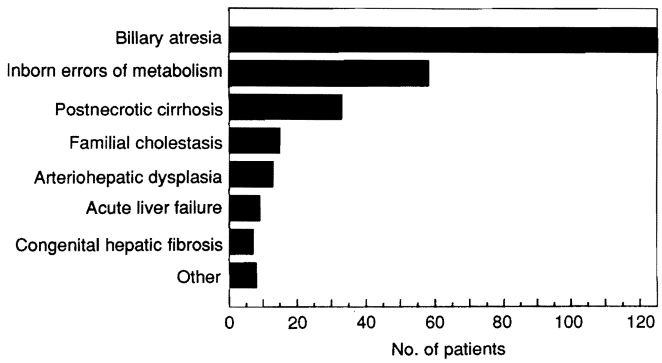

Fig. 1. Indications for liver transplantation in 268 pediatric patients (March 1980 to September 1986)

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Table 1. Clinical and laboratory features in 13 children with arteriohepatic dysplasia

	Present	Absent	Not stated
Abnormal face	9	2	2
Xanthomas	3	4	6
Growth retardation	13	–	–
Pulmonary artery stenosis	13	–	–
Vertebral anomalies	3	3	7
Paucity of interlobular bile ductules	13	–	–
Posterior embryotoxon	3	1	9

Table 2. Causes of death after liver transplantation in children with arteriohepatic dysplasia

Contributing factor	Cause of death	No. of patients
Hepatic artery thrombosis	1 – Bacterial septicemia (Citrobacter freundii) 2 – Disseminated CMV	2
Pulmonary hypertension and congenital severe right ventricular hypertrophy	Acute myocardial infarct	1
Portal vein thrombosis and biliary strictures	Bacterial septicemia (staphylococcal sepsis)	1
Severe biventricular cardiac hypertrophy, right atrial dilatation and generalized endocardial fibrosis	Cardiovascular collapse and intracerebral hemorrhage	1
Anatomic venous anomaly	Brain death (acute ischemic injury)	1

Table 3. Morbidity and mortality after transplantation according to the type of surgical procedure at the time of investigation for cholestasis

	No. of patients	Alive	Mortality		No. of grafts	Vascular thrombosis allograft
			< 30 days	> 30 days		
Portocholecystostomy	3	1	1	1	4	2[a]
Portoenterostomy	4	1	1	2	6	2
Other procedures without dissection of porta hepatis	6	5	1	0	7	2[b]

[a] One of the two was a portal vein thrombosis
[b] The two episodes of thrombosis occurred in the same patient, one in the first and the other in the second allograft

before the operation, showed residual subpulmonic stenosis and pulmonary valvular stenosis, but there was a drop in the right ventricular (RV) pressure from 200 to 100 mm Hg (no other data are available).

The technique for OLT has been described previously [12]. During the surgical procedure, the patients were monitored via electrocardiograms, intraluminal arterial pressure, central venous pressure (CVP), urine output, and core temperature. In addition, hematocrits, blood gases, electrolytes (sodium potassium and ionized calcium), prothrombin and partial thromboplastin times, and platelets were measured every hour or whenever required. Pulmonary artery pressure and cardiac output were not monitored in any of the cases.

Preoperative clinical status

The typical features of AHD syndrome are listed in Table 1. At the time of transplantation, all 13 children were jaundiced, 11 had pruritus, and 4 had ascites. Demineralizing bone disease was present in 7 patients, absent in 4, and unknown in 2. Four children had previous gastrointestinal bleeding, secondary to portal hypertension, and 3 had a history of encephalopathy. The histology of the native liver showed a variable degree of portal and bridging fibrosis and, in three cases, established cirrhosis was present.

Five of the 13 patients had relatives (parents or siblings) with cardiovascular or hepatic anomalies compatible with varying degrees of penetrance of AHD.

Age at the time of transplantation varied from 2 to 17.5 years and was related to the previous surgical procedure. The four patients with a previous classical portoenterostomy had a mean age of 2.6 years (range 2–3 years), while the others had a mean age of 7.6 years (range 2–17.5 years). The difference in age at the time of transplantation between patients with a portoenterostomy and portocholecystostomy and patients having had surgical procedures without dissection of the porta hepatis was also important (3.5 vs 9 years).

Laboratory data

Total bilirubin varied from 6.8 to 56.4 mg/dl (mean 22.2 mg/dl), more than half being conjugated. The SGPT ranged from 18 to 352 IU/l (mean 175 IU/l) and the SGOT from 126 to 1647 IU/l (mean 419 IU/l). The alkaline phosphatase levels ranged from 386 to 2920 IU/l (mean 1213 IU/l) while the gamma glutamyl transferase levels ranged from 63 to 2810 IU/l (mean 695 IU/l). Prothrombin time was moderately elevated in only two patients, and albumin ranged from 2.2 to 4.8 g/l (mean 3.5 g/l).

Statistical analysis

The values are given as mean and standard deviations. Patient survival was calculated using the life table method with the BMDP/PC (BMDP Statistical Software, Los Angeles, Calif. [4]).

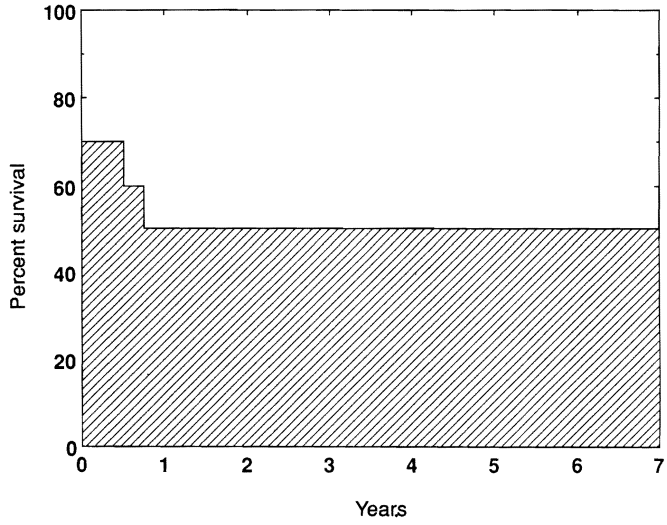

Fig. 2. Actuarial survival of 13 liver transplant recipients for arteriohepatic dysplasia

Results

Seven of the 13 transplanted patients are alive with a projected 1- and 7-year survival rate of 52% (Fig. 2). This is lower than that in children transplanted for other forms of liver disease [5]. The causes of death are listed in Table 2. Vascular complications were responsible for the deaths of three patients, and two other patients died during the initial postoperative period of heart failure and circulatory collapse, probably secondary to pulmonary hypertension and congenital heart disease. Based on the available clinical data, the severity of the pulmonary artery hypertension in these two patients could not be determined, nor could it be compared with that of the other patients. Analysis of intraoperative data shows some differences. The amount of crystalloid infusion in the two patients who died of heart failure was similar to that in the rest of the group: 15 ± 4.2 ml/kg per hour and 16.4 ± 11.6 ml/kg per hour, respectively. Likewise, the amount of blood and blood products transfused in the patients who died was 25.4 ± 11.2 ml/kg per hour compared to 27.9 ± 16.7 ml/kg per hour for the remaining group. The CVP of the two patients who developed heart failure was higher than that in the rest of the group. The difference in the CVP reading was present throughout the entire procedure. At the beginning, these two patients had a mean CVP of 16 ± 2.8 versus 10.3 ± 1.9 cm of water in the remaining group, and just before hepatectomy of 14 ± 1.41 versus 9 ± 3.3 cm of water in the other patients. There were no apparent differences in the mean arterial pressure or oxygenation until minutes before overt heart failure occurred.

The postmortem examination of one of these two patients demonstrated pulmonic stenosis with hypoplasia of the left pulmonary artery, a small ventricular septal defect, and severe right ventricular hypertrophy with focal interstitial fibrosis. In the other patient, a biventricular cardiac hypertrophy with right atrial dilatation and generalized endocardial fibrosis was observed.

Morbidity and mortality after liver transplantation, according to the type of initial surgical exploration for cholestasis, are shown in Table 3. Only two out of seven patients who had extensive hilar dissection at the time of the initial exploration are alive (28.6%), compared to five out of six patients who had no dissection of the porta hepatis (83.3%). This survival rate of 28.6% in the AHD patients with previous hilar dissection was worse than that of liver transplant recipients for extra hepatic biliary atresia (EHBA) and previous portoenterostomy (63%) transplanted during the same period of time.

Vascular complications in AHD occurred in 6 out of 17 grafts and consisted of thrombosis of the hepatic artery in 5 instances (29%) and thrombosis of the portal vein in 1 case (6%). No arterial thrombosis was observed in the six patients who had an end-to-end anastomosis of the donor and recipient hepatic artery. Alternative methods of arterial reconstruction were used in the other patients because of the presence of unsuitable vessels in the donor or recipient or both. The incidence of thrombosis in the latter group was 45% (5 out of 11 grafts). In this group, thrombosis occurred in four out of five (80%) aortic conduits (donor aorta in continuity with celiac axis) and in one out of six (16.6%) iliac artery grafts.

The incidence of arterial thrombosis in AHD was then compared to that in a group, similar in age and weight, of 86 patients with EHBA who were transplanted during the same period of time. In the EHBA group, there were five intraoperative deaths (5.8%), compared to two out of seven (28%) in AHD patients with prior extensive hilar dissection. Excluding those five patients, the incidence of arterial thrombosis in the EHBA group was 23 out of 98 allografts, or 23.5%. The incidence of thrombosis, using aortic conduits in EHBA, was 27.3%.

Four patients with AHD required retransplantation and one of these patients received three grafts. The indications for retransplantation were hepatic artery thrombosis in three instances and chronic rejection in the other.

Infection was the ultimate cause of death in 3 of the 13 patients. In one, sepsis was clearly opportunistic (disseminated cytomegalovirus infection); in the other two, the infection followed vascular thrombosis (staphylococcal sepsis in the patient with portal vein thrombosis and citrobacter freundii sepsis in another patient with arterial thrombosis). An anomalous venous return of the superior vena cava was the cause of death in another patient. At autopsy the findings were an absent superior vena cava with drainage of both innominate veins into the inferior vena cava below the renal veins. During the anhepatic phase, when the inferior vena cava was crossclamped for about 40 min, extreme venous hypertension in the craniofacial area developed, which caused irreversible brain damage and death 2 days later.

The seven surviving patients are well and free of jaundice, with a mean bilirubin of 0.5 mg/dl (range 0.3–1.2 mg/dl). The follow-up period ranges from 3.5 to 7 years. One patient has abnormally elevated transaminases and alkaline phosphatase (SGOT 119 IU/l, SGPT 130 IU/l, alkaline phosphatase 1018 IU/l), due to ischemic intrahepatic biliary strictures after thrombosis of the hepatic artery. This child requires balloon dilatation occasionally. All children are growing well and participate in normal childhood activities. Children of school age are attending school without any problems.

Discussion

Although AHD is usually a benign disease, a small group of patients develop cirrhosis. It has been suggested that a portoenterostomy could lead to early liver failure as a result of relapsing cholangitis [8]. Our data support this concept. Children having portoenterostomies or portocholecystostomies required liver transplantation at an earlier age than children with no biliary tract operations. Although age may not influence survival, it does influence the number of postoperative complications [6]. The mortality and incidence of vascular complications were very high in the AHD patients with previous hilar dissection, and certainly higher than those of the patients with EHBA. It is difficult to explain the difference in the incidence of thrombosis between the AHD patients and those with EHBA since both groups had previous hilar

operations and were similar in age and weight. The type of arterial reconstruction (aortic conduit) used in most of these Alagille patients for the arterial revascularization of the liver have been abandoned at our institution because of the associated high incidence of thrombosis. Instead, iliac artery grafts are used when circumstances call for an alternative method of reconstruction [10]. Moreover, a low flow state, due to a decreased cardiac output secondary to cardiovascular instability, may have predisposed the AHD patients to more episodes of vascular thrombosis; unfortunately, data were not available to prove or refute this hypothesis.

The two episodes of heart failure suggest that cardiopulmonary vascular anomalies may be a significant risk factor during the strenuous surgical intervention for liver replacement, particularly during the anhepatic phase. The high CVP in these two patients may have represented some degree of cardiac dysfunction since the amount of fluid administered during the OLT was similar to that in the rest of the group. In these two children the use of venous bypass might have prevented the hemodynamic compromise during the anhepatic phase. Venous bypass is not used routinely for pediatric liver transplantation in Pittsburgh because infants and small children tolerate venous occlusion and the anhepatic state reasonably well, certainly much better than adults [7]. Moreover, it is difficult to obtain adequate flow ratio; therefore, the risk of thrombosis and embolism may be high. Presently, in our institution, we do not use the bypass in children under 12 kg because a "piggyback" procedure is safely performed most of the time [13]. Preoperative evaluation of AHD patients must include cardiac catheterization (especially in patients with a documented RV hypertrophy) since assessment of cardiovascular hemodynamics with noninvasive studies may not be conclusive. We excluded a patient with AHD from OLT because of severe pulmonary hypertension, determined by cardiac catheterization. The clinical evaluation of this patient, including an echocardiogram, was unremarkable, with the latter only showing mild RV hypertrophy. In the past, this patient would have been submitted to a life-threatening intervention. Moreover, in our center, we are presently reluctant to perform an OLT in patients with an ejection fraction smaller than 40 %.

Because of the greatly improved quality of life experienced by surviving patients, the use of OLT for patients with end-stage liver failure due to AHD is the treatment of choice. A significant number of patients with AHD will not develop cirrhosis and their long-term prognosis is good [3]. Although only three patients in our study had cirrhosis at the time of OLT, in the other patients the indications for OLT were related to a progressive portal fibrosis, severe and permanent cholestasis, growth retardation, failure of the medical therapy to control the complications of the disease, and frequent and prolonged hospitalizations in the recent past as a consequence of progressive liver dysfunction. Survival may be enhanced by avoiding unnecessary biliary drainage procedures prior to transplantation. In the absence of portoenterostomy, the clinical course of patients with AHD and normal or hypoplastic extrahepatic ducts is usually benign. Cholestasis may persist and may often be severe, but it becomes a minimal clinical problem with increasing age [9]. In these patients, bile flow is not enhanced with a portoenterostomy. In contrast, cholangitis is a significant complication of portoenterostomy, which could lead to the onset of cirrhosis early in life [9]. Careful preoperative evaluation and intraoperative monitoring with a pulmonary artery catheter, maintaining a meticulous fluid balance, and the judicious use of vasoactive drugs may prevent some of the cardiopulmonary complications observed in AHD children following liver transplantation. Finally, recent experience with the use of an iliac artery graft (instead of an aortic conduit) to arterialize the liver when a direct anastomosis to the recipient hepatic artery is not possible has reduced the incidence of arterial thrombosis with the subsequent related morbidity and mortality.

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