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Liver Transplantation for Alagille's Syndrome

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• Twenty-three children with Alagille's syndrome and end-stage liver disease underwent liver transplantation with cyclosporine and low-dose steroid immunosuppression. Two to 9 years (mean, 4.4 years) after surgery, 13 (57%) of the children were still alive, with normal liver function. Three of the fatalities were due to cardiovascular failure secondary to associated cardiopulmonary disease. Mortality was higher among patients who had more severe cardiac disease and patients who had previously undergone a Kasai procedure. Although it has a higher than average risk, liver transplantation can be efficacious in patients with Alagille's syndrome and end-stage liver disease.

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The Watson-Alagille syndrome, also known as arteriohepatic dysplasia, is characterized by paucity of intrahepatic bile ducts and congenital cardiovascular anomalies.[1] It is inherited by an autosomal-dominant gene with reduced penetrance and variable expressivity. Clinical features include retarded growth, dysmorphic facies, ocular and cardiovascular anomalies (peripheral pulmonary stenosis mainly), neonatal cholestasis, mental retardation, skeletal malformations, and xanthomas.[2,3] Portal fibrosis reportedly occurs in 13.7% of the patients. Complications of liver disease are thought to be responsible for the deaths of 5% of the patients and constitute an indication for liver transplantation.[4-7]

In this retrospective study the courses of patients with Alagille's syndrome who underwent orthotopic liver transplantation with cyclosporine and low-dose steroids at the University of Pittsburgh (Pa) were reviewed to identify factors that may influence the postoperative prognosis.

PATIENTS AND METHODS

From March 1980 to October 1989, 475 children underwent orthotopic liver transplantation at the Children's Hospital of Pittsburgh. In 23 (5%) of these patients the underlying primary disease was Alagille's syndrome.

All 23 patients underwent a preoperative cardiac evaluation consisting of physical and ultrasonographic examination by a pediatric cardiologist. Right ventricular pressures were estimated by Doppler interrogation of the tricuspid valve regurgitation jet. Seven patients (30%) underwent cardiac catheterization. On the basis of the Doppler examination, cardiopulmonary disease was classified as mild if the estimated peak right ventricular pressure was lower than half the systemic peak pressure and severe if it was three fourths or more the systemic peak pressure. Cases between mild and severe were classified as moderate.

If cardiac catheterization was performed, cardiopulmonary disease was classified as mild if the mean right atrial pressure was 0 to 5 mm Hg, moderate if 5 through 10 mm Hg, and severe if greater than 10 mm Hg.

RESULTS

Preoperative Evaluation

The typical features of the syndrome identified in our 23 patients are listed in Table 1. During the first 2 months of life 21 patients underwent surgical exploration for jaundice, which revealed intrahepatic disease in 11 (52%) of these patients. Liver biopsy specimens obtained at the time were pathognomonic of arteriohepatic dysplasia in five patients (24%). In the remaining 16 patients (76%) the histologic findings were consistent with cholestasis. The diagnosis was confirmed with liver histologic features, revealing the paucity of interlobular bile ductules and the presence of pulmonary artery stenosis. There was a positive family history for Alagille's syndrome in 13 patients.

In five (50%) of the 10 children who died after surgery the pathognomonic findings of Alagille's syndrome were confirmed at autopsy. Autopsy was not performed in the remaining cases. Secondary or less common features of the syndrome were also looked for and identified on clinical or postmortem examinations. Ten patients underwent a Kasai procedure (portoenterostomy), presumably due to misdiagnosis. Two patients did not undergo exploratory laparotomy because the diagnosis was established with a combination of characteristic clinical features and percutaneous needle liver biopsy.

At the time of transplantation all 23 children (13 male [57%] and 10 female [43%]) were jaundiced, with total bilirubin levels ranging from 84 to 958 μmol/L (mean value, 455 μmol/L), 12 (52%) had ascites, and seven (30%) had a history of variceal bleeding. In 11 patients (48%) recent liver histologic features were diagnostic of cirrhosis, whereas the remaining 12 patients (52%) were found to have bridging fibrosis. The histopathologic evaluation of the hepatectomy specimens revealed severe cholestasis in

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all 23 patients and established cirrhosis in 11 patients (48%). No malignancy was identified in any patient.

Ages of the patients at the time of transplantation ranged from 6 months to 17.5 years, with a mean age of 5.0 years. Patients who had previously undergone a Kasai procedure had a mean age of 3.8 years at transplantation (range, 2 months to 6.5 years), whereas the non-Kasai group (n=13) had a mean age of 6.2 years (range, 2 to 17.5 years).

Postoperative Course

With follow-up ranging from 2 to 9 years (mean follow-up, 4.4 years), 13 (57%) of 23 patients receiving transplants are alive to date. Overall mortality (43.5%) was higher than in the contemporaneous general population of pediatric liver transplant recipients (35.6%).[4-7] Four patients (17.4%) died of hepatic artery thrombosis, one (4.3%) of portal vein thrombosis, three (13%) of cardiovascular complications, one (4.3%) of an opportunistic infection, and one (4.3%) of primary graft nonfunction. Tables 2 and 3 summarize the relationship of the clinical characteristics of these patients to outcome after liver transplantation. Sepsis was the terminal cause of death in six patients (26%).

Eight children (35%) required retransplantation. One received three grafts and was alive 4 years later. The overall mortality after retransplantation was 75% (six of eight patients died). The cause of graft failure was hepatic artery thrombosis in eight cases, viral hepatitis in two cases, portal vein thrombosis in one case, and rejection in one case.

The 13 surviving children are to date free of jaundice and clinical or laboratory findings of liver failure.

Table 1.—Findings in 23 Patients Undergoing Liver Transplantation for Alagille's Syndrome

Finding	No. (%) of Patients (N=23)
Intrahepatic bile duct paucity and cholestasis	23 (100)
Cardiovascular anomalies with pulmonary artery stenosis as the main component	23 (100)
Dysmorphic facies	15 (65)
Psychomotor retardation	14 (61)
Skeletal malformations	11 (48)*
Ocular abnormalities (posterior embryotoxon)	10 (43.5)
Xanthomas	6 (26)

COMMENT

Watson-Alagille syndrome is reportedly accompanied by liver cirrhosis in 12% to 14% of cases.[8,9] The downhill course is usually slow, allowing for proper evaluation and timely transplantation in these children, if needed.[2,3,10] Indications for transplantation include impending liver failure, usually manifested by rapidly deepening jaundice and portal hypertension, particularly if complicated by severe bleeding or hypersplenism or ascites nonresponsive to conservative treatment. Nonfatal complications, such as failure to thrive or severe itching, may compromise the child's life enough to prompt transplantation.

Our study was limited to the experience from the cyclosporine era to provide a homogeneous group with follow-up of more than 2 years.

Skepticism on the eligibility of these patients for liver transplantation is mainly focused on the increased perioperative risk due to associated cardiopulmonary abnormalities. Our study demonstrates that, in fact, patients with cardiopulmonary anomalies are at increased risk after liver transplantation compared with average controls. Three of the deaths were due to heart failure secondary to preexisting cardiopulmonary disease. Other factors pre-

Table 2.—Patients' Clinical Characteristics as Determinants of Mortality

Characteristic	No. (%) of Patients (N=23)	No. of Deaths (% of Patients)
Age, y		
<5	14 (61)	8 (57)
≥5	9 (39)	2 (22)
Body weight, kg		
<13	17 (74)	9 (53)
≥13	6 (26)	1 (17)
Total preoperative bilirubin level, μmol/L		
<257	9 (39)	3 (33)
≥257	14 (61)	7 (50)
Portal hypertension	12 (52)	6 (50)
Without portal hypertension	11 (48)	4 (36)
Previous Kasai procedure	10 (43)	7 (70)
Without previous Kasai procedure	13 (57)	3 (23)
Peripheral pulmonary artery stenosis only	17 (74)	7 (41)
Multiple cardiopulmonary anomalies	6 (26)	3 (50)

Table 3.—Cardiovascular Anomalies as Determinants of Mortality

Type of Cardiovascular Anomalies	No. of Patients With Mild Disease/ No. (%) of Patients Who Died	No. of Patients With Moderate Disease/No. (%) of Patients Who Died	No. of Patients With Severe Disease/No. (%) of Patients Who Died	No. of Deaths due to Cardiac Complications
Peripheral pulmonary artery stenosis only	9/2 (22)	8/5 (62)	0	1*
Peripheral pulmonary artery stenosis and other cardiac defects†	3/1 (33)	1/0	2/2 (100)	2‡

*This patient had moderate disease.

†Cardiac defects included pulmonary valve stenosis in four patients; atrial septal defects in three patients; and pulmonary venous stenosis, bicuspid aortic valve, and coarctations of the aorta in one patient each.

‡Both of these patients had severe disease.

disposing to increased mortality in our series included previous portoenterostomy, young age, low weight, and high bilirubin levels; due to the small sample size, however, none of these factors achieved statistical significance.

The value of thorough cardiopulmonary evaluation cannot be overemphasized. Preoperative cardiac Doppler examinations should be performed routinely. Cardiac catheterization should be performed if the results of the Doppler study are not conclusive. Patients with severe cardiopulmonary abnormalities tolerate the anhepatic phase of the transplantation better with the use of extracorporeal venovenous bypass. If this is not feasible, the use of the piggyback technique[11] combined with a temporary portacaval shunt, as recently suggested, may alleviate the hemodynamic changes and assist in better survival.[12]

Heart, lung, and liver transplantation may be the only solution for patients with end-stage disease who are deemed incapable of receiving transplants due to the severity of the underlying cardiac disease.

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ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Peripheral Primitive Neuroectodermal Tumors: A Flow Cytometric Analysis With Immunohistochemical and Ultrastructural Observations

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Flow cytometry of classical neuroblastoma has provided provocative evidence that cell cycle and ploidy analysis generate prognostically useful information. To determine whether such analyses of peripheral primitive neuroectodermal tumors might yield similar results, formalin-fixed, paraffin-embedded tissue specimens from 19 peripheral primitive neuroectodermal tumors, each previously characterized by immunohistochemical or ultrastructural study, were assessed. An acceptable histogram was obtained in 16 cases. Of these, nine neoplasms were diploid and seven contained aneuploid DNA. Among patients with diploid lesions, four were free of disease, whereas three had persistent or recurrent disease, and two had died of tumor. Among patients with aneuploid neoplasms, four were free of disease, one had recurrence, and two had died. There was no apparent correlation between immunophenotype and proliferative activity with the clinical outcome. Among aneuploid peripheral primitive neuroectodermal tumors, DNA index did not predict survival. Hence, cell cycle and DNA ploidy analyses do not appear to contribute to the prognostic assessment of peripheral primitive neuroectodermal tumors, as they do to presumably related neoplasms of the central and peripheral nervous system (*Arch Pathol Lab Med.* 1992;116:1202-1208).

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