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ORIGINAL ARTICLE

Characteristics and Outcome of Liver Transplantation in Children with Alagille Syndrome: A Single-center Experience

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Key Words
Alagille syndrome;
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Background: This study was carried out in Chang Gung Memorial Hospital-Kaohsiung Medical Center, Taiwan, with the aim of reviewing the characteristics and the outcome of liver transplantation (LT) in children with Alagille syndrome (AGS).
Methods: We performed a retrospective analysis of transplant records of children diagnosed with AGS and undergoing LT between 1987 and 2010.
Results: Nine patients underwent living donor LT. Cholestasis and characteristic facies were seen in all patients. Posterior embryotoxon was seen in 4/9 (44.4%), butterfly vertebrae in 3/9 (33.3%), heart defect (pulmonary stenosis in 2) in 3/9 (33.3%), and renal disease in 2/9 (22.2%) patients. Five cases had cholestasis prior to the age of 60 days, whereas four cases had cholestasis after 60 days of age. Iminodiacetic acid scans showed no excretion of isotope into the bowel in four cases and suggested a false diagnosis of biliary atresia. All patients underwent diagnostic laparotomy and liver biopsy. Results of liver biopsy showed characteristic features of paucity of interlobular bile ducts in all patients. Kasai portoenterostomy was not performed in any patient prior to being referred for LT. The mean age at the time of LT was 4.6 years. The 5-year overall survival rate after living donor LT was 88.9%.

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Conclusion: Our conclusion is that the clinical features of AGS are informative. In addition, histological confirmation is important in the diagnosis. AGS children with severe liver disease had good prognoses with LT.

1. Introduction

Alagille syndrome (AGS), biliary atresia, choledochal cysts, and gallbladder disease can be associated with similar clinical symptoms, laboratory findings, and radiographic findings that make accurate diagnosis difficult.[1] All of these conditions/diseases can be associated with high morbidity and mortality if the diagnosis and treatment are not accurately provided or they are delayed.[1]

AGS is an autosomal dominant disorder.[2] In addition to the liver, AGS is also associated with abnormalities involving the heart, eye, skeleton, and kidney, and the increasing importance of abnormalities in the central nervous system is being recognized.[2,3] Cholestasis associated with AGS may, in a few cases, be extremely severe and result in a major impairment in the quality of life during early childhood, eventually resulting in cirrhosis.[4] It is reported that pruritus and xanthomata disappear and results of liver function tests are normal in 83.3% of AGS children after living donor liver transplantation (LDLT).[4] The overall 20-year average survival rate is 70% after LDLT.[5] These results indicate that the quality of life can be improved after LT in children with a severe hepatic form of AGS.[4]

In this study, we reviewed our experience with AGS, its signs and symptoms, diagnostic modalities, and outcome after LDLT.

2. Patients and Methods

The medical records of patients diagnosed as AGS and those AGS patients who underwent LDLT at Chang Gung Memorial Hospital-Kaohsiung Medical Center, Taiwan, between 1987 and 2010 were retrospectively reviewed. This study was approved by the Technical Review Board and Ethics Committee of Chang Gung Memorial Hospital.

All patients had at least three of the five major clinical features (chronic cholestasis, congenital heart disease, "butterfly-like" vertebrae, posterior embryotoxon, and peculiar facies). End-stage liver disease was clinically defined by the following laboratory tests: serum bilirubin concentration >17.0 mg/dL and prolonged prothrombin time despite judicious treatment with parenteral vitamin K. Investigations for portal hypertension included ultrasonography and computed tomography angiography and/or conventional angiography. Therapy included various antipruritus drugs over time and supplementation as necessary with parenteral or oral fat-soluble vitamins.

Baseline immunosuppression involved cyclosporine (Neoral) administration (600 mg/m^2/day for pediatric patients and 15 mg/kg/day for adults). The C2 concentrations were aimed at 800—1200 ng/mL during the first 6 months, 640—960 ng/mL for up to 1 year, and 480—720 ng/mL thereafter. Intravenous methylprednisolone or oral prednisolone was administered when tolerated, and azathioprine (2 mg/kg/day) was discontinued when the patient had not experienced an episode of severe rejection in the preceding 6 months. All of the acute rejections were reversed with steroid pulse therapy.[6] Mycophenolate (Roche, Basel, Switzerland) was used in recipients whose indications included a more potent immunosuppression and renal-sparing benefits.[7]

2.1. Statistical analyses

Data were expressed as mean ± standard deviation or median (range). Survival rates were calculated according to the Kaplan—Meier method and the results were compared using the log-rank test. All significance tests were two tailed and differences were considered to be statistically significant at $p < 0.05$. Statistical analyses were performed using SPSS version 10 (SPSS Inc., Chicago, IL, USA).

3. Results

Twelve cases were diagnosed with AGS. Nine of the 12 underwent LDLT. Two were brothers who underwent LDLT and received partial liver allograft. Cholestasis and characteristic facies were seen in all of the patients. Posterior embryotoxon was seen in 4/9 (44.4%) patients and butterfly vertebrae in 3/9 (33.3%) patients. Heart defect (2 with peripheral pulmonary stenosis and 1 with atrial septal defect) was seen in 3/9 (33.3%) patients and hepatopulmonary syndrome in 2/9 (22.2%) prior to LDLT. Upper gastrointestinal bleeding was observed in 3/9 (33.3%) and one had hepatic artery occlusion. Iminodiacetic acid scans showed no excretion of isotope into the bowel after 24 hours in 4/9 cases (44.4%). Four cases had cholestasis after 60 days of age, whereas five cases had cholestasis prior to 60 days of age. A small gallbladder on ultrasonography (<1.5 cm length) was noted in 3/9 cases (33.3%); 4/9 cases (44.4%) showed no excretion of isotope into the bowel, which suggested a false diagnosis of biliary atresia. Liver biopsy is needed in all cholestasis cases especially in those cases where biliary atresia cannot be excluded. All underwent diagnostic laparotomy and liver biopsy. Liver biopsy showed characteristic features of paucity of interlobular bile ducts in all patients. Kasai portoenterostomy was not performed in any patient prior to being referred for LT.

The mean age at the time of LDLT was 4.6 years (range: 1.0—10.6 years). The total serum bilirubin ranged from 2.0 mg/dL to 15.1 mg/dL. Indications for LT in patients with AGS were refractory pruritus in all of the nine children, decompensated cirrhosis in seven patients, recurrent