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

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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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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. 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. AGS is an autosomal dominant disorder. 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. 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. 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). The overall 20-year average survival rate is 70% after LDLT. These results indicate that the quality of life can be improved after LT in children with a severe hepatic form of AGS.

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 anti-pruritus drugs over time and supplementation as necessary with parenteral or oral fat-soluble vitamins.

Baseline immunosuppression involved cyclosporine (Neoral) administration (600 mg/m²/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. Mycophenolate (Roche, Basel, Switzerland) was used in recipients whose indications included a more potent immunosuppression and renal-sparing benefits.

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
upper gastrointestinal bleeding in four patients, and hepato-pulmonary syndrome in two patients. Four cases had somatic growth retardation prior to LDLT and one died after LDLT; the other three cases caught up in lineal growth after LDLT. The first one weighed 11.8 kg (3–10 percentile) at 3 years of age; at 4 years and 5 months of age, the child’s height was 103 cm (10–25 percentile) and weight was 16 kg (10–25 percentile). The second child weighed 9.0 kg (<3 percentile) at 2 years and 9 months of age; at 12 years of age, the patient’s height was 141.6 cm (10–25 percentile) and weight was 34 kg (10–25 percentile). The third one was 8 kg (<3 percentile) at 1 year, and 153 cm (10–25 percentile) in length with 45 kg (10–25 percentile) at 16 years 5 months old. Renal disease prior to LDLT existed in 2/9 (22.2%) patients.

The 5-year and 20-year overall survival rates after LDLT were 88.9% and 77.8%, respectively. Patient follow-up ranged from 4.3 years to 25.7 years after transplant (Figure 1). The two deaths occurred within the first 30 days after LDLT. One case died due to hepatic artery thrombosis, whereas the other died from gastrointestinal bleeding complicated with intracranial bleeding complicated with brain herniation.

### 4. Discussion

Neonatal cholestatic jaundice is mostly caused by neonatal giant cell hepatitis. Biliary atresia and AGS also present as neonatal cholestatic jaundice (8% and 6%, respectively). Persistent cholestatic jaundice is associated with poorer survival with native liver. The correct treatment for each of these clinical entities is different and can significantly reduce morbidity and mortality from these diseases. The findings of microcornea, posterior embryotoxon, and anomalous optic discs should suggest the diagnosis of AGS. Liver biopsy shows characteristic features of paucity of interlobular bile ducts in 76.6%. In our nine cases, 44.4% had abnormal findings in the eye, but all showed the paucity of interlobular bile ducts and peculiar facies. This suggests that performing careful physical examination looking for peculiar characteristics and liver biopsy findings of interlobular bile duct paucity are important to diagnose AGS.

Four cases had cholestasis after 60 days of age. The other five AGS cases had cholestasis prior to the age of 60 days with three children having small gallbladders and four patients without excretion of isotope into the bowel, making it difficult to exclude biliary atresia from the diagnosis of AGS. The Kasai procedure, although appropriate for children with biliary atresia, does not benefit children with AGS and actually appears to worsen outcomes. None of our patients had Kasai’s operation. A correct diagnosis can avoid an unnecessary Kasai portoenterostomy. It is reported that mutations in JAG1 can be identified in 70% of AGS patients. However, we did not do genetic profiling studies. We emphasized the importance of the peculiar facies and liver pathology in the diagnosis of AGS.

In a large series of AGS, heart defects were present in 107 of 117 (91.5%) patients with peripheral pulmonary stenosis as the most common condition. Complex congenital heart disease and hepatic disease with or without LT contribute significantly to AGS mortality. There were reported cases of mitral valve regurgitation requiring valvuloplasty, anomalous origin of the left coronary artery from the pulmonary artery, and severe aortic stenosis. As reported previously, the frequency of complex cardiac anomalies was lower in the LT group with AGS compared with published AGS series (5% and 13%, respectively). We did not see these complex heart conditions in our cases with routine two-dimensional trans-thoracic echocardiography evaluation prior to LT. The lower prevalence of complex cardiac anomalies in LT could result from selection criteria for transplantation candidates or the small number of AGS patients in our study. This needs further study to be clarified. We had three congenital heart disease patients, one atrial septal defect and two peripheral pulmonary stenosis cases. The causes of death of our patients were without cardiac manifestations of AGS disease, which is different from previous reports.

Actuarial survival rates with the native liver were 51% and 38% at 10 years and 20 years, respectively. The common factors contributing to the decision for LT were bone fractures, pruritus, and severe xanthomata. Most AGS patients undergo LT at a median age of 6.5 years, which is consistent with our study where two cases died after LDLT within 30 days. LDLT is efficacious treatment modality for AGS. The overall survival rate was 80.4% at 5 years and 62% at 20 years. Tannuri et al reported that AGS constituted 3.3% of all indications for LDLT in Brazil. Most patients undergo LT at a median age of 6.5 years. Liver dysfunction improved in all successful cases.

We should also be careful when procuring partial liver grafts from close family relatives of AGS patients as these donors may be AGS patients who were diagnosed. In a
previous study, the donor operation had to be aborted because of a liver biopsy that showed paucity of bile ducts during the operation. However, such a finding was not found in liver pathological analysis in this study.

In summary, we report the clinical characteristics of nine AGS patients with severe liver disease who had a good 5-year overall survival rate after LT. The clinical features of AGS are informative. Histological confirmation is important in the diagnosis.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

References