Liver Transplantation in Polish Children With α_1-Antitrypsin Deficiency: A Single-Center Experience

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ABSTRACT

Background. α_1-Antitrypsin deficiency (ATD) is the most common genetic cause of liver injury in young children. Asymptomatic hepatitis is observed in most patients. However, the course of liver disease due to ATD is unpredictable, and some children develop liver cirrhosis. Liver transplantation (Ltx) dramatically improves their outcome and in some cases is required in the first years of life. The aim of the study was to evaluate the course of the disease in children with ATD treated with Ltx in a single center.

Methods. We retrospectively reviewed the clinical features (ascites, esophageal varices, esophageal bleeding) and laboratory parameters of liver function in children with ATD who were treated with Ltx.

Results. Twenty-two Ltxs were performed in 20 children (13 boys, 7 girls). Median age at transplantation was 12 years (range 0.5 to 17.1). Four children were transplanted in the first 2 years of life and 16 patients were over 7 years old. The indications for Ltx in younger children were progressive cholestasis with coagulopathy and ascites. In older patients, the indications were as follows: liver failure presenting with variceal bleeding in 7 patients, ascites in 5 patients, hypersplenism in all but 1 patient. In the group of children transplanted over 7 years old, the frequency of cholestasis decreased intermittently in the second year of life: 4 patients (25%) compared to 15 patients (94%) and 10 patients (63%) in the neonatal and pre-transplant period, respectively. In the group of children transplanted earlier, cholestasis and hepatitis were maintained until Ltx. Of transplanted patients, 50% were malnourished at the transplantation, and 50% were followed for more than 10 years. Five-year post-transplant survival was 100% (n = 14), and 10-year survival was 90%. Two patients died as adults with biliary post-transplant complications and problems with compliance.

Conclusions. Our experience suggests that transient normalization of liver parameters in some patients with ATD do not exclude the liver disease progression to cirrhosis and unfavorable outcome of liver disease in childhood. In our group of patients, median age at transplantation was high compared to other centers. The long-term prognosis in children after transplantation is very good, but early post-transplant complications and probable problems with compliance in young adults may lead to graft failure.

α_1-ANTITRYPSIN deficiency (ATD) is one of the most common genetic disorders in the Caucasian population, with an incidence in European countries of 1/4727 [1], but the prevalence varies markedly from one country to another and occurs in about 1/9110 [2] in Poland. The codominantly inherited defect is associated with liver and

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lung manifestations. The liver disease observed in 10% to 15% of PiZZ homozygotes is caused by accumulation of misfolded α_1-antitrypsin in the endoplasmic reticulum of hepatocytes and may lead to liver cirrhosis. In northern Europe, ATD is the second most common indication for liver transplantation (Ltx) after biliary atresia and the most common genetic cause of Ltx in children. The most common presenting symptom is prolonged cholestatic jaundice, often with pale stools and hepatitis. More than 80% of transplanted children present with neonatal hepatitis [3]. Before the era of Ltx, the mortality rate for end-stage liver disease in children with ATD 10 years after the onset of the disease was 28%. Because we do not have effective treatment for liver damage in ATD, Ltx remains the only therapeutic option for end-stage liver disease. The results of Ltx in this group of patients are good.

The aim of the study was to evaluate retrospectively the course of liver disease in children with ATD and Ltx based on our single-center experience.

METHODS

Between 1982 and 2015, 168 children with liver problems due to PiZZ phenotype of ATD were assessed in our department. They were admitted from other centers with hepatomegaly, hypertransaminasemia, or neonatal cholestasis.

We retrospectively analyzed the data from 1982 to 2015 on children with PiZZ phenotype of ATD observed in our center. Children with abnormal liver tests were initially diagnosed to have ATD by low concentration of α_1-antitrypsin in serum and by PiZZ phenotyping. During this time, 19 PiZZ patients and 1 with PiSZ phenotype developed end-stage liver disease and required Ltx. Ltx has been available in our center since 1990. We analyzed laboratory parameters and clinical symptoms of liver dysfunction (ascites, esophageal varices, esophageal bleeding) in the neonatal period, in the second year of age, and in pretransplant period in patients treated with Ltx. For this study, we used data from our hospital notes and laboratory records. Current information on present status of transplanted patients was obtained in most cases from their families and from Poltransplant registry.

RESULTS

During the past 30 years, we followed 167 children with ATD PiZZ in our department. A bad course of the disease was observed in 23 patients (14%) with PiZZ and 1 patient with PiMZ phenotype. Four boys died of liver cirrhosis with coagulopathy, 3 of whom had variceal bleeding followed by multiorgan failure before Ltx was available. One child was disqualified from getting a liver transplant for severe developmental delay and died of variceal bleeding.

Twenty patients were transplanted between January 1995 and October 2015 (22 Ltx): 15 patients in our center, 2 in Hospital Necker-Enfants Malades, 1 in Beaujon Hospital in Paris, 2 in Universite Catholique de Louvain in Brussels. All patients were Caucasian, and 13 (65%) were boys. Median age at diagnosis was 0.17 years (range 0.08 to 16 years). All children but 1 presented with neonatal hepatitis (95%); 10 patients had atresia-like symptoms.

Table 1. Pretransplant Clinical Features of 20 Patients With Alpha-1-Antitrypsin Deficiency Treated With Liver Transplantation

Clinical Features	Value
Ascites (1/0), n (%)	8 (40%)
Splenomegaly (1/0), n (%)	18 (90%)
Esophageal varices (1/0), n (%)	17 (85%)
Gastrointestinal bleeding (1/0), n (%)	7 (35%)
Jaundice (bilirubin >1.2 mg/dL), n (%)	14 (70%)
Encephalopathy, n (%)	1 (5%)
Prior abdominal surgery, n (%)	7 (35%)
Male, n (%)	13 (65%)
Weight (kg), median (min- max)	37.7 (5.8–64)
Living donor, n (%)	10 (50%)
Age at Ltx (y), median (min-max)	12 (0.5–17.1)

Seven children underwent prior abdominal surgery: operative revision of the biliary tract in 3 patients and hepatoportoenterostomy in 4 children (Table 1). The median age at transplantation in the whole group was 12.2 years (range 0.5 to 17 years), but during the last 12 years median age was 8.3 years. In the group of 4 children who underwent Kasai procedure, the median age of transplantation was 13.7 years (range 0.5 to 17). Organs were obtained from cadaveric donors (whole livers) in 50% of the children. Of the 20 children, 4 (20%) were transplanted in the first 2 years of life and 16 (80%) were over 7 years old at the transplantation. The indications for Ltx in 4 younger children were progressive cholestasis with coagulopathy and ascites. In 16 older children, the indications were as follows: liver failure presenting with variceal bleeding in 7 patients, ascites in 5 patients, and hypersplenism in all but 1 patient. Ascites and coagulopathy were first symptoms of liver disease in 16-year-old boy. Encephalopathy was observed in a 7-year-old girl with portal hypertension.

In the group of children transplanted after 7 years of age, the frequency of cholestasis decreased intermittently in the second year of life: 4 patients (25%) vs 15 patients (94%) vs 10 patients (63%) in the neonatal and pretransplant period, respectively. In the group of children transplanted earlier, cholestasis and hepatitis were maintained until Ltx (Table 2). Pretransplant laboratory values of our patients are shown in Table 3. At the time of transplantation, 50% of patients were malnourished. Median weight at the time of transplantation was 37.8 kg (range: 5.8 to 64 kg), and 9 of 20 patients (45%) were below the third percentile.

Follow-up after Ltx was 7 years (range: 1 month to 18.3 years). Ten patients (50%) were followed for more than 10 years. Short-term complications included revision of the hepatic artery in 2 patients and portal thrombosis in 1 child. Biliary leak with drainage of biliary collection was found in 8 pts (40%) and was the major short-term complication. Biliary stenosis with recurrent infections was observed in 3 patients and was treated with radiologic dilatations. Cyclosporine and azathioprine were used for immunosuppression