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Liver transplantation for alpha-1-antitrypsin deficiency in children

Andreas A. Prachalias
Mohamed Kalife
Ruggiero Francavilla
Paolo Muiesan
Anil Dhawan
Alastair Baker
Dino Hadzic
Giorgina Mieli-Vergani
Mohamed Rela
Nigel D. Heaton

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A.A. Prachalias · M. Kalife · R. Francavilla
P. Muiesan · A. Dhawan · A. Baker
D. Hadzic · G. Mieli-Vergani · M. Rela
N. D. Heaton
Liver Transplant Surgical Service,
Paediatric Liver Service,
King's College Hospital, Denmark Hill,
London SE5 9RS, UK

N.D. Heaton (✉)
Liver Transplant Surgical Service,
King's College Hospital, Denmark Hill,
London SE5 9RS, UK
Tel.: + 44-17-1737-4000 4801
Fax: + 44-17-1346-3574

Abstract Alpha-1-antitrypsin (a1-AT) deficiency is an inborn error of metabolism, which can cause liver disease. The condition is one of the most common genetic disorders in the Caucasian population. Here we review our experience with 21 children suffering from end-stage liver disease due to a1-AT deficiency. All children are PIZZ homozygotes. Nineteen of them initially presented with neonatal jaundice and two with hepatosplenomegaly in childhood. Twenty-five liver transplantions were performed. All children are currently alive at a median follow-up of 40 months. Liver replacement provides the only definite treatment for children with end-stage liver disease associated with a1-AT deficiency. Excellent results can be achieved by reducing waiting time for transplantation and by early referral to a liver transplant centre.

Key words Alpha-1-antitrypsin deficiency · Liver transplantation · Childhood

Introduction

Alpha-1-antitrypsin (a1-AT) deficiency is a co-dominantly-inherited disorder which can cause liver disease. Affected patients usually present in early infancy with liver disease or emphysema in adult life [9]. The disease is one of the most common genetic disorders in the Caucasian population with an incidence of 1:1639–2000 live births [11]. Alpha-1-antitrypsin is a glycoprotein with antiprotease activity which is synthesized primarily in the hepatocytes but is also produced in mononuclear phagocytes and neutrophils. It inactivates neutrophil elastase, trypsin and other proteolytic enzymes. Serum deficiency of a1-AT is due to a single gene mutation at chromosome 14 [9]. At present, more than 75 variants have been described, but only a few are clinically significant. Two relatively common phenotypes, PISS and PIZZ produce low serum concentrations of alpha-1-antitrypsin: PISS homozygotes produce about 60% and PIZZ homozygotes about 15% of normal levels, while the PI null phenotype produces no detectable serum levels.

Ineffective inhibition of neutrophil elastase by a1-AT causes alveolar elastin destruction, which is thought to produce emphysema. The cause of the liver injury is unknown. Only a small proportion (17%) of PIZZ homozygotes develop liver disease and, of these, only a minority progress to cirrhosis and liver failure [19]. Lomas et al have proposed that Z antitrypsin in PIZZ phenotype undergoes a loop-sheet polymerization into the endoplasmic reticulum which results in blocked protein transport from the reticulum to the Golgi with subsequent protein accumulation which injures the liver [7].

For patients with liver disease secondary to a1-AT deficiency who progress to cirrhosis and liver failure, there is at present no other specific treatment than liver replacement.

We report a single centre's experience of liver transplantation for a1-AT deficiency in children.

Table 1 Clinical features of children with liver disease related to alpha-1-antitrypsin deficiency ($n = 21$)

	No.	%
Jaundice (bilirubin > 20 μmol/l)	16	76.1
Hepato-splenomegaly	15	71.4
Ascites	14	66.6
Oesophageal varices	9	42.8
Gastrointestinal Bleeding	6	28.5
Encephalopathy	1	9.5

Table 2 Laboratory findings at the time of listing for transplantation. (*INR* International normalized ratio, *GGT* Gamma glutamyl transpeptidase)

	Median and range	Normal values
Haemoglobin (g/dl)	10.8 (8.2–13.4)	11.5–15.5
INR	1.38 (0.97–4.6)	0.9–1.2
Creatinine (μmol/l)	40 (23–92)	< 80
Total bilirubin (μmol/l)	41.5 (3–957)	3–20
Alkaline phosphatase	513 (87–915)	< 350
GGT (IU/l)	176 (4.48–723)	5–55
Albumin (g/l)	32 (19–40)	35–50

Materials and methods

Between November 1989 and December 1997, 261 children received 302 liver transplants at our institution. During this period, 21 children with end-stage liver disease secondary to a1-AT deficiency underwent 25 liver transplantations. Cases were identified from our clinical database and information was retrieved from clinical notes and laboratory records. There were 13 males and 8 females, median age 3 years (range: 0,6–15), median weight 17,5 kg (range: 5–64), at the time of transplantation. Eight of these children (38%) were below the 25th centile (5 below the 4th) at the time of transplantation. The diagnosis of a1-AT deficiency was established by the presence of PIZZ phenotype as determined by detecting abnormal mobility of alpha-1-antitrypsin by isoelectric focusing [1].

All patients underwent standard pre-transplant assessment. Donor- and recipient operations were performed according to surgical techniques previously described [21]. Standard triple therapy with cyclosporine, prednisolone (2 mg/kg) and azathioprine (2 mg/kg) was used for immunosuppression. Acute rejection episodes were treated with pulse steroids for 3 days (methyl-prednisolone 10 mg/kg). Tacrolimus (Prograf) was administered to in patients with acute rejection not responding to steroids, as a rescue therapy for chronic rejection and to those children who underwent retransplantation.

Results

Twenty-five liver transplants were performed in 21 children with end-stage liver disease related to a1-AT deficiency, in addition, one child also had cystic fibrosis. The diagnosis of a1-AT deficiency was established before six months of age in 19 and over the age of 5 years in 2 children. The first sign of liver disease in 19 was jaundice within the first 8 weeks of life whilst hepatosplenomegaly was the first sign in the 2 children older than 5 years. The clinical features prior to liver transplantation are shown in Table 1. Eighteen patients (85,7%) developed clinical signs of portal hypertension. The laboratory data of these children at the time of pre-transplant assessment are shown in Table 2.

At the time of diagnosis, the histopathological findings were consistent with chronic liver disease secondary to a1-AT deficiency [3, 4]. All patients were PIZZ homozygotes. A family history of a1-AT deficiency was identified in 6 cases (28.5%); of these, 5 were siblings and 1 was of a PIZZ homozygote mother, without evidence of liver disease. The decision to list for transplantation was taken when the child developed signs of hepatic decompensation with persistent hypoalbuminaemia, or ascites, increasing jaundice, coagulopathy, not responsive to vitamin K and/or variceal bleeding. The time elapsed from diagnosis to listing for transplantation ranged from 1–168 months (mean 52.1 months). This time tended to be longer (72.6 vs. 52.1 months) in those patients with a positive family history. The average waiting time from listing to transplantation was 46 days (range: 25 days –5 months). Organs were obtained from blood group matched cadaveric donors. The median age and body weight of donors were 14 years (range: 2–42) and 42.5 kg (range: 13.3–95), respectively. Of the 25 transplants, 14 were whole, and 11 were reduced-size grafts. Of the reduced-size grafts, 6 were left lateral segments (5 from split-livers) and 5 were right lobes (one from a split-liver). Biliary reconstruction was achieved via a Roux-en-Y hepatico-jejunostomy in all but one case, in which an end-to-end choledoco-choledocostomy was performed. The median graft cold ishemic time was 12.25 h (range: 8–19.5 h). The median blood loss was 1,490 ml (range: 200–9,180) or 80 ml/kg. There was no statistically significant difference in weight-adjusted blood loss between whole grafts and cut-down livers. The median operating time was 6 h (range: 4.25–7). One child who was found to have both a1-AT deficiency and cystic fibrosis presented with cholestasis from birth. He underwent transplantation 2 months after diagnosis, at the age of 9 months.

Three patients underwent a total of four re-transplants. The indication for re-transplantation was hepatic artery thrombosis in two children, early (day 11) in one and late in the other (4 months post-transplant). One child was re-transplanted twice for chronic rejection and is well 8 years post-transplant with good graft function. This patient has also developed liver, kidney microsomal type 1 positive autoimmune hepatitis post-transplant [6], which has responded to steroid therapy. Four children required additional post-transplant surgery for wound dehiscence, small bowel obstruction secondary to adhesions (in two cases), hepatic artery reconstruction after early thrombosis noted on postopera-

tive day 3 (without further complications). An early cut surface bile leak in a left lateral segment graft settled with conservative management.

The overall incidence of hepatic artery thrombosis (HAT) was 14.3%. Two out of three children with HAT were less than 5 years old (6 months and 3 years old) and had received whole liver grafts. Arterial inflow in these two was provided from the recipient's common hepatic artery. The third child with HAT was 15 years old and received the right lobe of a split-liver graft with arterial inflow from recipient's common hepatic artery and was successfully revascularised with an iliac conduit.

Medical complications included ten culture proven bacterial infections from line sepsis in 4 cases, respiratory infection in 5 cases, and liver abscess in a patient with a late hepatic artery thrombosis. There were 5 CMV infections in three patients, including CMV-hepatitis on two occasions and seroconversion in three. Thirty biopsy proven acute rejection episodes were encountered in 13 children and treated with pulse steroids successfully in all but six cases (28.5%) which were converted from cyclosporine to tacrolimus because of resistance to steroid treatment. To date, all 21 children are alive at a median follow-up of 40 months (range 3–97 months). One child has evidence of chronic rejection with progressive liver damage. Seven patients (33.3%) developed hypertension post-transplant, which was transient in three, whilst four still remain on long-term anti-hypertensive therapy.

Discussion

Alpha-1-antitrypsin deficiency is the most common inborn error of metabolism causing liver disease. Liver disease associated with PIZZ phenotype accounts for 8% of patients attending our tertiary pediatric liver service [9]. The course of the disease is variable, ranging from cholestasis with potential recovery to progression to chronic liver disease. Of the children with PIZZ, 10–20% are reported to develop advanced liver disease on histological criteria if neonatal hepatitis is present in the first months of life [19,18]. The uncertainty regarding disease progression is reflected in this series by the wide range of time elapsing between the diagnosis and listing for transplantation, and has led several authors to emphasize the difficulty in the selection and timing of transplantation [3,20]. It has been proposed that the appropriate time is when signs of hepatic failure or decompensation begin to appear. Thus, persistent or recurrent jaundice has been associated with poor prognosis, while paucity of the interlobular bile ducts on liver biopsy has been considered both as a good [12] and a poor prognostic feature [3,4]. The timing of transplantation remains difficult. Persistent hypoalbuminaemia, the presence of ascites, persistent jaundice, coagulopathy not responsive to vitamin K and/or variceal bleeding were indications for transplantation. These parameters have previously been shown to be associated with poor prognosis and death from within two weeks to four years [12]. The need for early transplantation in patients with a1-AT deficiency, as an effort to minimize post-operative complications, has been emphasized [5]. Although it has been previously reported that portacaval shunt may prevent complications of portal hypertension in a1-AT deficiency children with preserved synthetic function [17], this approach has been applied only in a few cases and has not gained wide acceptance [2]. None of the patients in this series had been considered for surgical shunt prior to transplantation, owing to the perceived risk of encephalopathy after the procedure.

Since the first report of successful liver transplantation for a1-AT deficiency associated liver disease [13], results have steadily improved with reported 3-year patient survival of 83 to 94% [2, 3]. Replacement of the cirrhotic liver results in acquisition of the donor phenotype, a rise in serum levels of a1-AT and significant improvement in the quality of life [3,20]. In this series, all children are currently alive at a median follow-up of 40 months with a graft survival of 84%. These results can be attributed to the extensive application of reduction, split-liver and living-related techniques in our unit [15] leading to a short median waiting time (45.6 days). Thus, transplantation was carried out in the majority of cases before there was a severe deterioration in general health. In the present series all children but one underwent transplantation electively from home. Early referral to a liver transplant centre is particularly helpful in optimizing the timing of transplantation.

Post-transplant complications for patients with a1-AT deficiency were no different from those observed in other children post- liver transplant. The incidence of HAT in this group of patients was slightly higher than that reported by other authors and in our series overall (7%). Esquivel et al reported an incidence of 13.7% [2], Filipponi et al 12,5% [3] and Vennarecci et al 7.7% [20]. This higher incidence may be due to the lower median age of our patients (3 years) and the use of whole grafts in two small children [14]. It is also known that alpha-1-antitrypsin is important for maintaining the integrity of blood vessel walls, and possibly the condition itself gives rise to weakness of the arterial wall and disruption at the time of vessel clamping during transplantation [16].

The hypertension observed in seven patients (33%) in this series was less common than the incidence of 71.5% previously reported [10] and was treated with standard anti-hypertensive agents. The co-existence of a1-AT deficiency and cystic fibrosis has been reported previously and appears to increase the risk for persistent

neonatal jaundice [8] and, from our experience, may lead to early transplantation.

In conclusion, for those children with a1-AT deficiency who develop end-stage liver disease, liver transplantation is, to date, the only definite treatment. The results of liver transplantation are excellent with the application of surgical techniques which expand the donor pool and therefore reduce the waiting time for a suitable organ. Emphasis still needs to be placed on the careful selection of those children who will require transplantation in the future, in order to minimize post-transplant morbidity and mortality.

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