Case Report

Living-related liver transplantation

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ABSTRACT

We report here, the first pediatric living-related liver transplant in Saudi Arabia and the Middle East. Our patient is a 2 year old girl with a diagnosis of progressive familial intrahepatic cholestasis, causing intractable pruritis and failure to thrive requiring liver transplantation. The child was successfully transplanted using a segment of her mother's liver for living-related liver transplantation. Two years post-transplantation the patient is doing well. With the ongoing crises in cadaveric organ availability and the high prevalence of pediatric liver disease, living related liver transplantation is an ideal solution to this difficult and challenging problem.

Keywords: Liver, living-related liver transplantation, progressive familial intrahepatic cholestasis, pruritis, organ donation.

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Over the last decade the spectrum of liver disease in children has broadened with improved diagnostic modalities. Liver transplantation stands out as the only life saving treatment for end-stage and progressive liver disease and enables survival in the majority of patients with previously fatal illnesses.[1] Awareness of the benefits of liver transplantation plays a major role in expanding the patient waiting list. However, despite various educational measures, cadaveric donor organ availability has not increased, especially in small children. Ten percent to 25% of pediatric candidates on the waiting list in North America as compared with 100% in Saudi Arabia still die because of the shortage of organs.[2] The crisis in organ supply which has affected the adult programs has shaped the evolution of living related pediatric liver transplantation. Moreover, in countries where brain death criteria are not established and people have poor perception of the idea of organ donation, living related liver transplantation (LRLT) is the only therapeutic option.

The adult cadaveric whole-liver transplant program in Saudi Arabia commenced in 1990.[3] However, because of the scarcity of cadaveric donors, living related liver transplantation is the ideal alternative for the pediatric age group. At the Riyadh Armed Forces Hospital, we report the first pediatric liver transplant from a living donor. Since the program's inception, 10 successful LRLT cases have been performed, establishing it as the first and only program of its kind in the Arab world.

Case Report. Our patient is a 27 month old Saudi girl, product of full term normal pregnancy and cesarean section delivery to a 27 year old mother. Her symptoms started at the age of 3 months when she was noticed to be jaundiced and diagnosed as a case of neonatal hepatitis. Subsequently she developed intractable pruritis resistant to medical treatment and was growing poorly. She was first referred to our hospital at the age of 2 years for further management. The child did not have any history of melena, hematemesis or chronic diarrhea. At the time of her presentation the parents' main concern was the severe pruritis interfering with the patient's and the family's quality of life, to the extent that the child was continuously inserting stones in her

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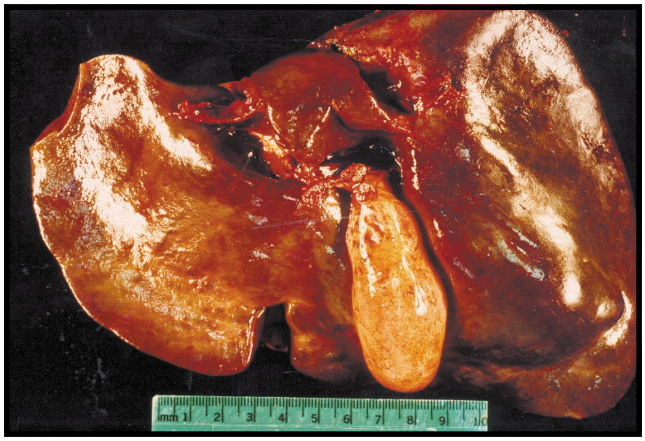

Figure 1 - The above picture illustrates the dorsal aspect of the recipient liver.

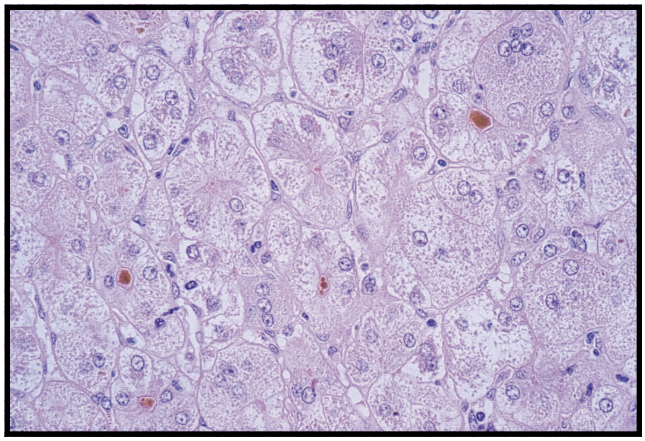

Figure 2 - The liver cells show pseudorosettes around bile plugs with occasional giant cell formation.

ear canal to scratch it. There was a family history of two cousins who died, one in infancy and one in early childhood, with a similar disease.

On physical examination the child was deeply jaundiced with multiple scratch marks all over her body. Her weight was 9kg below the third centile, her height was 75cm on the 3rd centile and her head circumference was 49cm on the 50th centile. Her spleen was enlarged to 2cm b.c.m. and her liver was enlarged with a total span of 16cm. There was no ascites, other signs of chronic liver disease or rickets. She was not walking at the time of her presentation. The results of her investigations showed a normal full blood count, urea, creatinine and electrolytes. Total bilirubin was 168 µmol/l (normal:0-22) with a direct of 126 µmol/l. Her liver enzymes, alkaline phosphatase 1152 IU/l, aspartate transaminase 1530 IU/l and alanine transaminase 310 IU/l were elevated, with the exception of gamaglutamyl transpeptidase which was 14 IU/l (normal:7-32). Serum bile acids were elevated up to 412 µmol/l (NL:0-8.9). Prothrombin time was 14 seconds (control = 14 seconds) and partial thromboplastin time was 34 seconds (control 32 seconds), albumin, cholesterol and triglycerides levels were normal. Blood pyruvate, lactate, a1-antitrypsin and serum amino acids chromatography were normal. No organic acids or reducing substances were detected in the urine. Infectious screen for hepatitis A, B, C, human immunodeficiency virus and TORCH infections were all negative. Serum zinc at 8 µmol/l (NL: 11-18 µmol/l), vitamin E < 2 µmol/l (NL:14-44) and 25Hydroxy vitamin D at 13.4 nmol/l (NL:33-92) were all low. Abdominal ultrasound showed increased echogenicity of the enlarged liver. Doppler ultrasound showed patent liver vessels. The hepatectomy specimen showed non-cirrhotic liver with intact normal gallbladder (Figure 1). Under light microscopy however, the liver cells showed

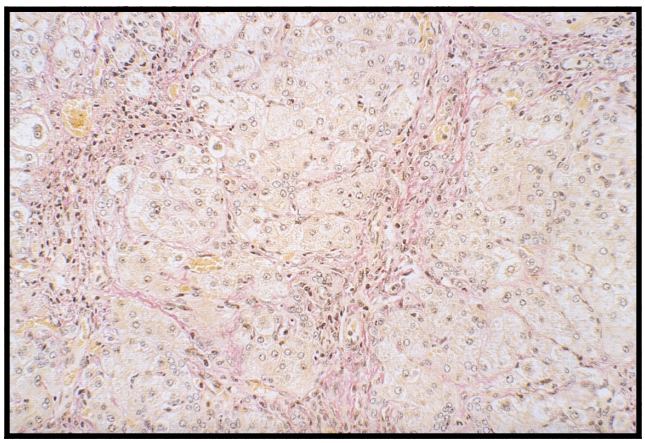

Figure 3 - The above picture illustrates significant portal fibrosis with septal formation (Evg x 100).

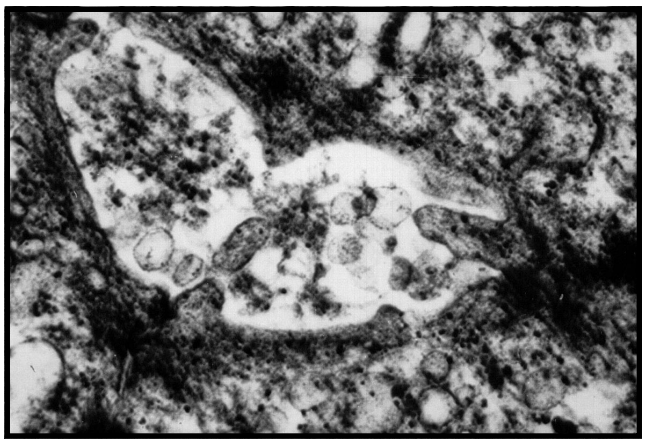

Figure 4 - The lumen of the bile canaliculuc is distended by coarsely granular bile. Microvilli are scant and the basement membrane is thickened. (Osmium tetroxide/uranyl acetate/ lead citrate original magnification 24 X 500).

ballooning with occasional giant cells and significant bile plugs (Figure 2). Portal fibrosis with extensive bridging was also noted (Figure 3). Under electron microscopy the examination of the bile canaliculi revealed scanty minocillin with thick basement membrane and course granular bile (Figure 4). The constellation of chronic cholestasis, pruritis, normal gamaglutamyl transpeptidase, elevated level of bile acids, the evidence of giant cell hepatitis and the positive family history led to the diagnosis of progressive familial intrahepatic cholestasis. The child underwent, successfully, liver transplantation from a living related donor (her mother).

Donor. The patient's mother, a healthy 27 year old, was evaluated for living-related donation. She had no history of heart or liver disease, nor any other significant past medical history. Her physical examination was within normal limits. Her laboratory evaluation included CBC, clotting screening, electrolytes, blood urea nitrogen, creatinine, total bilirubin, conjugated bilirubin, gamaglutamyl transpeptidase, alkaline phosphatase, alanine amino transaminase and aspartate amino transpherase which were all normal. She had positive Imunoglobuling G for cytomegalovirus and Epstein Barr virus. Hepatitis B and C screens were negative. Abdominal computer tomography showed left lateral segment of the liver to be 265mls. Angiography was performed and showed normal anatomy of the liver vasculature.

Operative procedure. A left lateral hepatectomy was performed on the mother. After total hepatectomy an orthotopic liver transplant was performed on the child. The detailed operative technique will be mentioned elsewhere.

Post-operative course. The mother's recovery course was unremarkable. The child's post-operative course was smooth. She was started on methylprednisolone and cyclosporin. Target level of cyclosporin was 80-140 µg/ml. In the first 48 hours after surgery, liver enzymes increased secondary to prolonged warm ischemia time (76 minutes) but normalized within one week. By then, her pruritis had resolved and one month after liver transplantation she was walking. On the 20th day following transplantation, the patient became febrile and the liver enzymes were mildly elevated. AST = 53IU/L, ALT = 85 IU/L, GGT = 93 IU/L. Infection was ruled out and rejection was suspected. She was treated with pulse methylprednisolone therapy for 3 days with no improvement in liver enzymes at that time. Histological biopsy of the liver confirmed the diagnosis of rejection. Since we had difficulty in maintaining cyclosporin levels within therapeutic range, and with the poor response to steroids, we decided to change her medication to FK506. The target level for FK506 was 10-15 µg/ml. Liver enzymes normalized 5 days after starting FK506. The patient was discharged in good condition 60 days after the transplant. At one year follow-up, liver enzymes (AST = 25 IU/L, ALT = 30 IU/L, GGT=22 IU/L) are still normal with an FK level of 6-8 µg/ml since discharge.

Discussion. LRLT provides improved survival in the pediatric liver transplant recipient. Since 1980 continued improvements have led to an overall 1 year survival rate of 80%-90% in children.[4,5] This improvement in survival can be attributed to several factors, such as the decrease in cold ischemic time, the theoretical graft matching and improved health and stability of the donor. The ability to perform an elective liver transplant allows definitive treatment of the liver disease prior to significant deterioration of the recipient's general medical condition. The critical factors that indicate a need for transplant can be categorised within the following framework of general indications:[6,7] primary liver disease that is expected to progress to hepatic failure; non-progressive liver disease with morbidity that outweighs the risks associated with transplantation; primary therapy for liver-based metabolic disease fulminant hepatic failure of known or unknown atiology; complications causing intolerably poor quality of life rather than likelihood of death. One particular example in the last cited category is intractable pruritis which was the case in our patient. The patient was suffering from progressive familial intrahepatic cholestatis syndrome (PFIC), previously known as Byler's Syndrome, which is an inherited progressive liver disease ending in cirrhosis.[8,9] Children suffering from this condition are at risk of dying from fulminant infections in early childhood. The quality of life of our child and her family improved dramatically as noticed during her regular follow-up visits. Her pruritis resolved totally and her growth picked up to the 25th centile and she was able to walk one month after liver transplantation. Her parents are pleased with her progress and a normal family relationship has been restored. Strict follow-up has contributed to her improved outcome. Life-long single immunosuppressive therapy is imperative in such patients.[10-13] The ethical dilemma of subjecting a healthy donor to a major surgical procedure was an obstacle that was overcome. The evidence of a substantially low risk to the donor has been derived from results of hepatic resections for benign liver disease in comparable cohorts of patients. The advanced surgical experience and optimal intensive care management contribute to a good outcome with a calculable risk for the donor of less than 0.4%.[14-16] The selection of a donor is based on the following criteria: blood relation to the recipient; blood group compatibility; relatively young age; absence of risk factors (e.g. smoking, oral contraceptive use, hypertension, diabetes mellitus, cardiac disease); absence of infectious diseases such

as hepatitis B, C and human immunodeficiency virus; detailed thorough psychological assessment; signed informed consent.[17-19] The left lateral lobe of the liver makes up 20% of the total liver volume. By the end of the first year post-operatively, a regeneration rate of up to 80% is expected in the donor liver.[20] In our donor, liver function tests were normal within a week post-operatively and remain so. No other late complications developed in our patient.

In conclusion, living related liver transplantation (LRLT) is a remarkable innovation that has had a major impact in pediatrics. Important factors must be kept in mind, however, if the application of transplantation is to be consistent with the best medical interests of the patient. In our population, metabolic liver disease prevails secondary to a high rate of consanguineous marriages. With the increasing constraints, partly financial, in sending patients abroad for treatment, a living-related liver transplant programme is a priority in the Kingdom. Survival rate following LRLT is 80%-90% as compared with the almost 100% morbidity rate associated with end-stage liver disease.

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