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Pediatric living-donor liver transplantation

Mureo Kasahara*, Seisuke Sakamoto, Akinari Fukuda

Organ Transplantation Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo, Japan

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ABSTRACT

Living-donor liver transplantation is an important component of all liver transplant programs especially in those that care for the pediatric population. Over the last 30 years, innovations in surgical technique have converted living donation from an experimental procedure to a standard of care. Many of these innovations occurred in countries where culturally, deceased donation is limited leaving no alternatives but living donation. The Organ Transplantation Center at the National Center for Child Health and Development (NCCHD) in Tokyo, Japan, was established in 2005 where we have generated some of those innovations and in so doing, have performed living-donor liver transplantation in over 400 children. Here we review the indications, technical details, and outcomes of that cohort.

Introduction

The concept of living-donor liver transplantation (LDLT), using a part of the liver from a healthy individual to treat another sick individual, dates to the mid-20th century. In the 1980s, when deceased whole organ liver transplantation (LT) became a universally available standard procedure, transplantation medicine faced the inevitable issue of organ shortage. Deceased donor organ shortage in the pediatric population led to the technical innovations of reduced-size and split-liver transplantation.[1,2] The emergence of LDLT as a special extension to the concept of split-liver transplantation was a natural consequence of these procedures. The major difference is that mortality/morbidity is unacceptable in living donors.

LDLT was introduced in Japan in 1989 as a life-saving procedure for a patient with biliary atresia due to the scarcity of organs available for deceased donor transplantation.[3] The shortage of deceased organ donors led to the development of unique technical, physiological, and logistical innovations in LDLT.[4,5] Experience with and technical improvements in living-donor surgery have led to the generalization of pediatric LDLT to adult LDLT with excellent patient and graft survival outcomes.[6] These techniques have expanded the potential donor pool and decreased waiting list mortality.[7] Graft alternatives have expanded from the left lateral segment (LLS) to the left lobe, right lobe, and modification of the left lateral segment for small infants.

The number of LDLTs performed in Japan increased to a peak of 562 in 2005 followed by a decrease and stabilization to approximately 400–450 annually (Figure 1). During the past 25 years, 7862 LDLTs were performed in Japan, 2897 were children less than 18 years of age. Over the past 5 years, the annual number of pediatric LDLT cases has been ~120–140. During the same period, 45 deceased LT, including 20 split-liver procedures in pediatric patients were performed.[8]

There have been technical and immunological refinements in the Japanese pediatric LDLT process, such as resolving graft size matching and overcoming blood type mismatches. The Kyoto group reported that the use of small-for-size grafts, defined as grafts with a graft-to-recipient body weight ratio (GRWR) less than 0.8%, is associated with small-for-size syndrome—the development of massive ascites, renal insufficiency, persistent cholestasis, coagulopathy, and infectious complications—in recipients resulting in reduced patient survival. The etiology of small for size is thought to be parenchymal cell injury and reduced metabolic and synthetic graft capacity due in part to portal vein overflow.[9] In contrast, large-for-size syndrome can occur in neonatal and infantile LDLT. The main problems associated with large-for-size grafts include the small size of the recipient's abdominal cavity, size discrepancies between vascular structures and insufficient blood supply to the graft. When GRWR is estimated to be over 4.0%, reduced or hyper-reduced LLS grafts have been introduced to mitigate the problems of large-for-size syndrome especially in the neonatal acute liver failure patient population.[10]

ABO-incompatible LDLT was introduced in Japan to overcome donor shortages. ABO-incompatible grafts were used in nearly 13% of the recipients included in the Japanese LDLT series. It has been reported that in the pediatric population, despite the application of preoperative plasma exchange, splenectomy, and enhanced immunosuppression, the 5-year graft survival rate is less than 70%. A Japanese LDLT series reported that ABO-incompatible liver

* Corresponding author.
E-mail address: kasahara-m@ncchd.go.jp (M. Kasahara).

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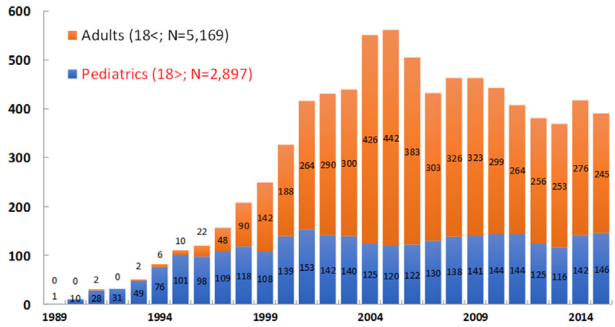

Fig. 1. Living-donor liver transplantation in Japan (1989–2015, $n = 7862$).

transplantations were performed with relative safety in infants less than 2 years of age, although the long-term results were not satisfactory in children over 2 years of age.[11,12] Patients over 10 years of age remain at considerable risk for early fatal outcomes due to complications such as hepatic necrosis and late ischemic cholangitis. New strategies to prevent antibody-mediated rejection are required.

The Organ Transplantation Center at the National Center for Child Health and Development (NCCHD), Tokyo, Japan, was established in 2005. We have generated a series of videos of our innovative surgical procedures encompassing standard and complicated case presentations and have shared them to anyone interested in our effort to standardize and improve the quality of surgery for end-stage liver disease (Pediatric Liver Surgery and Transplantation E-learning: Surgical Technique: http://www.ncchd.go.jp/recruitment/movie/organ_index.html, ID: seiiku-guest Password: otLEZYjC). We are grateful for our patients from whom we have learned so much.

NCCHD recipient experience

At NCCHD, we have performed 440 liver transplants, consisting of LDLT in 414 cases, deceased donor liver transplantation (DDLT) in 22, and domino liver transplantation in 4, for 426 recipients through the end of 2016. The median age at LT was 1.3 years (range: 18 days to 34 years). The underlying liver diseases for primary transplants included cholestatic liver diseases in 214 cases, metabolic liver diseases in 84, acute liver failure in 56, congenital hepatic fibrosis/Caroli disease in 26, liver tumors in 19, vascular diseases in 14, autoimmune liver diseases in 5, and the liver cirrhosis with undetermined etiology in 8 (Figure 2). Thirteen recipients underwent re-transplant, one of whom received the third graft. The characteristics and outcomes of the recipients with each liver disease are described below.

Cholestatic liver diseases

Biliary atresia (BA) was the most common cholestatic liver disease indication for LT, 193 cases (45.3%). All of the patients except 3 had undergone a previous Kasai procedure. The median age at LT was 11 months (range: 4 months to 34 years). One hundred and two cases underwent LT by the age of 2 years. The mean body weight was 14.0 ± 14.6 kg (range: 3.7–96.0). Thirty seven cases weighed less than 6.0 kg. The mean Pediatric End-Stage Liver Disease (PELD) score was 10.6 ± 8.9. Comorbid conditions included patients with congenital heart disease (CHD), situs inversus (SI), and portopulmonary hypertension. Seven recipients presented with CHD—atrial septal defect in 4 cases, ventricular septal defect in 2, and double-outlet right ventricle (DORV) in 1. The case with DORV underwent cardiac surgery to fix hemodynamic circulation and then successfully received LDLT. The cases with the other types of CHD underwent

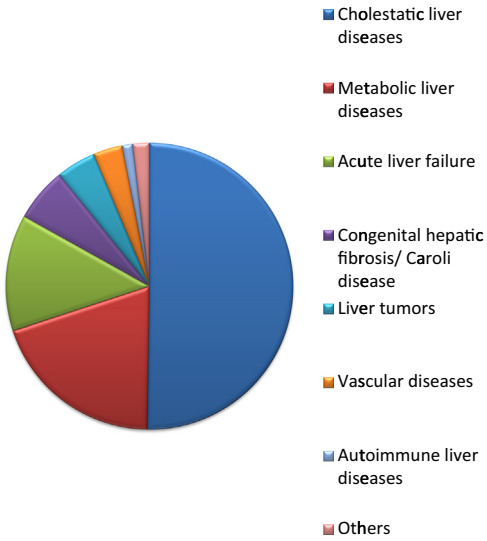

Fig. 2. NCCHD recipient underlying disease.

LT without cardiac surgery. All of the cases with CHD are doing well with good graft function. SI occurred in association with the polysplenia syndrome with malrotation, preduodenal PV, aberrant hepatic arterial supply, and absence of inferior vena cava (IVC) in 4 cases. Twenty one cases suffered from intrapulmonary shunting (IPS) and three cases had portopulmonary hypertension. The mean measurement of IPS rate, calculated by TcMAA pulmonary scintigraphy was 21.3 ± 6.7% (range: 16.0–39.0%). Four cases suffered from biliary strictures and one case had portal vein thrombosis, all of whom were successfully treated by radiological or surgical interventions. One BA case had a malignant tumor—a 30 year-old female was found on explant to have an incidental cholangiocarcinoma. Although her LDLT was successfully performed and adjuvant chemotherapy was immediately initiated, she developed multiple tumor recurrence 7 months after LDLT and did not survive.[13] Overall graft survival rates of BA cases at 1, 5, and 10 years were 95.8, 95.2, and 95.2%, respectively. As classified into 4 groups by the age at LT; infants (younger than 1 year, $n = 102$), young children (1–6 years, $n = 52$), school children (6–18 years, $n = 30$), and adults (older than 18 years, $n = 9$), the 5-year graft survival rate was 93.9%, 100%, 96.7%, and 77.8%, respectively.

Among the other cholestatic liver diseases, 8 cases with Alagille syndrome (AGS) underwent LDLT. All were genetically confirmed to have mutations of Jagged1, although 2 cases underwent a Kasai operation with a clinical diagnosis of BA. Eleven cases with progressive familial intrahepatic cholestasis (PFIC), including type 1 in 1 case and type 2 in 10 cases underwent LDLT.[14]

Metabolic liver diseases

Urea cycle disorders (UCD, $n = 27$, 32.1%), consisting of ornithine transcarbamylase deficiency (OTCD, $n = 18$) and carbamoyl phosphate synthetase 1 deficiency (CPS1D, $n = 9$), were the most common metabolic liver diseases indicated for LT.[15] The median age of OTCD at LT was 10 months (range: 3 months to 17 years) and that of CPS1D was 6 months (range: 4–10 months). The overall graft survival rate of UCD was 96.3% at 5 years. Three cases with UCD, 2 cases in OTCD and one case in CPS1D received hepatocyte transplantation in the neonatal period and then successfully underwent LDLT as bridge transplantation once their body weight reached 6.0 kg.[16] Although OTCD is an X-linked inheritance, the use of asymptomatic heterozygous donors has been accepted with careful examinations in LDLT. Two cases with OTCD, receiving grafts from their mothers, experienced severe