Pediatric Liver Transplantation in India: 22 Years and Counting

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Liver transplantation in India has grown exponentially in the last decade with 135 centers now performing between 1500-2000 transplants a year, 10% of which are pediatric. Survival rate surpassing 90% has been achieved, and India is now an important regional liver transplant hub in South and South-East Asia. The indications have expanded to include increasing number of liver-based metabolic disorders that may or may not cause liver disease. Recipients, who were previously considered non-transplantable such as those with pre-existing portal vein thrombosis, can be successfully managed with innovative microvascular techniques. The donor pool has grown with the use of marginal grafts and ABO incompatible organs. Financial constraints are being overcome by crowd funding and increasing philanthropic efforts.

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Liver transplant is curative for acute liver failure, chronic end stage liver diseases, some liver tumors and inborn metabolic errors that may or may not cause liver disease per se. Advancements in preoperative care, surgical techniques, intensive care management along with availability of potent immunosuppressive drugs have helped attain 94% 1-year, 91% 5-year, and 88% 10-year patient survival in pediatric liver transplant recipients [1]. In India, the first successful pediatric liver transplant was performed in 1998 [2], and that boy with biliary atresia is now about to complete his graduation in medicine and is doing well on minimal immunosuppression (***Table* I**). Every year around 1500-2000 liver transplants are now performed, of which approximately 10% are pediatric. Survival rates surpassing 90% have since been attained in India [3-5]. Initial progress was slow as part of a learning curve with limitations due to scarcity of trained personnel, poor awareness amongst primary care doctors, reservations regarding donor safety and the financial implications. By 2007, only 318 liver transplants had been performed in India [6]. The growth has been exponential in the last decade; although collated data of the country is not available. This has been sustained mainly by living donor liver transplant (LDLT) though deceased donation (DDLT) is picking up, primarily in the southern part of the country where some centers report a 70/30 LDLT/DDLT overall distribution [7]. As per the Global Observatory on Donation and Transplantation, 1945 liver transplants (adult and pediatric) were performed in India in the year 2018 (1313 LDLT).

Auxiliary liver transplant (auxiliary partial orthotopic liver transplant, APOLT) with implantation of a partial graft without fully removing the native liver is technically more challenging with a higher complication rate. It is a suitable option for acute liver failure and metabolic disorders without cirrhosis as it offers a chance for immunosuppression free life in case of native liver regeneration or restoration of defective metabolic function with newer therapies. Successful APOLT for acute liver failure has been reported from India but the modality has not become popular due to the higher risks

Table I History of Pediatric Liver Transplantation in India

Event	*Year*
Pediatric living donor liver transplant (LDLT)	1998
Adult deceased donation liver transplant (DDLT)	1998
Liver transplant for acute liver failure (ALF)	1999
Adult combined liver and kidney transplant	1999
Pediatric combined liver and kidney transplant	2007
Pediatric re-transplant	2002
Pediatric DDLT	2007
Liver transplant for HIV	2008
Liver transplant for Criggler-Najjar syndrome	2008
Domino transplant	2009
LDLT for factor VII deficiency	2010
Auxillary liver transplant for ALF	2012
ABO incompatible liver transplant	2014
Domino auxillary liver transplant	2015

involved with retaining a diseased liver in acute liver failure with its attendant toxic and metabolic effects.

The establishment of a new liver transplant program requires approval from a regional health body after evaluation of infrastructure and expertise. As per the National organ and tissue transplant organisation (NOTTO) there are now about 135 centers for liver transplant in India, including second tier cities apart from the metros, with majority of the pediatric work limited to about 10 centers (***Fig.* 1**). As liver transplant is largely private sector driven and is a high cost procedure, credibility rests on preventing commercialization of the programs. This has been made feasible by the stringiest criteria laid down by the government and strict scrutiny by authorization committees in every case to ensure donation is from a relative on a wholly voluntary basis with no coercion. In camera meetings are held and all documents to establish near relationship are verified before a go ahead is attained even in cases requiring emergency transplants.

A significant proportion of pediatric patients are from overseas. Patients from about 20 countries have been transplanted at our center, and also at other Indian centers. A few are partially or wholly funded by their governments, while many others raise funds through international charities and/or social organizations. Many families have gone on to form support groups in their respective countries. The Indian Human Organ Trans-plant Act, enacted in 1994, allows foreign nationals to receive a deceased organ in India only if no suitable Indian recipient is available. As cadaveric donations are few and the waiting list is long, foreign nationals would only qualify for LDLT.

India is now an important regional center for liver transplant in South and South East Asia, more so for pediatric patients. Many of these neighboring countries have either not yet set up transplant units or are in the fledgling phase running predominantly adult programs. Pediatric liver transplant carries its own set of challenges due to the smaller diameter of vessels requiring greater surgical expertise along with need for specialized pediatric intensive care and usually a longer duration of postoperative hospital stay. Moreover, many of these countries have very few pediatric hepatologists with expertise in post-transplant care, thus necessitating a thorough coordination with the transplant unit for follow up once the families travel back to their native countries.

EXPANDING THE DONOR AND RECIPIENT POOL

Though biliary atresia remains the leading indication for liver transplant in children [8], improving outcomes have encouraged expanding indications to include liver-based metabolic defects [9]. Where these defects cause liver

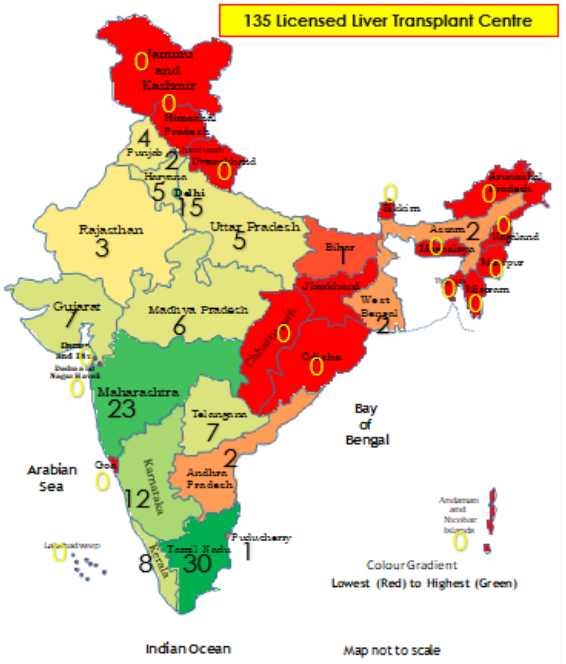

Fig. 1 *Distribution of liver transplantation centers in India, 2020.*

damage, liver transplant is curative by replacing the diseased organ as in other disorders of liver architecture leading to synthetic dysfunction and decompensation. The other group includes disorders whereby a genetically inherited enzymatic defect, wholly or partially liver based with a structurally normal liver, causes neurological/ multiorgan involvement that may be prevented by replacing the liver. Liver transplant should be performed early before irreversible damage occurs in target organs. These include Criggler Najjar syndrome, urea cycle defects and organic acidemias to achieve intact neurological status, familial hypercholesterolemia to prevent cardiac disease and/or sudden death, and primary hyperoxaluria where an early liver transplant prevents renal failure or else a combined/sequential liver kidney transplant would be required to prevent systemic oxalate overload and its multiorgan consequences. With the availability of next generation sequencing (NGS) based tests, precise and timely genetic diagnosis can now be made and timely therapy instituted.

Livers from patients with Maple syrup urine disease (MSUD) and familial hypercholesterolemia may be donated to cirrhotic patients as they are structurally and functionally normal apart from an enzyme deficiency, which may be compensated by other body tissues to sustain function. Such transplants, known as domino transplants, have been successfully reported from India [10]. As our programs are primarily living-related, the majority of the donors are parents who are carriers of the

recipients' metabolic or genetic disorders with autosomal recessive inheritance. Use of such heterozygous donors has been debated. Data from the Japanese multicenter registry [11] has reported that outcome after employing heterozygous donors was excellent with better long-term survival rate. Portal vein thrombosis (PVT), a known sequelae of cirrhosis, especially more frequently seen in infants with biliary atresia due to portal vein hypoplasia, is no longer a contraindication to liver transplant despite the technical difficulty and higher risks of post-transplant vascular thrombosis endangering the graft [12].

Pediatric liver transplant has now progressed beyond the ABO blood group barrier. ABO incompatible (ABOi) transplants are being increasingly performed when blood group compatible donor from the family is not available. Despite concerns about liver graft regeneration, antibody mediated rejection (AMR), higher incidence of biliary strictures and sepsis, both pediatric and adult ABOi liver transplant survival has improved markedly and has become comparable to ABO-compatible liver transplant with the introduction of rituximab prophylaxis before transplant [13]. Rituximab and/or other B cell desensitization strategies including plasmapheresis and IVIg are used to bring down isoagglutinin titers to less than 1/8 pre liver transplant. Children younger than 2 years of age may not require these desensitization therapies as blood group isoagglutinins titers are low and complement system activation is not robust, thus minimizing the risks of AMR [14]. ABOi liver transplant grafts in acute liver failure in infants have thus been used more often as lack of time window for desensitization strategies may limit use of this modality in older children and adults with acute liver failure [15]. Most busy centers in India have successfully performed ABOi transplants since the initial reports of success in 2014 [16].

Size-matching determined by the graft-to-recipient weight ratio (GRWR) is a crucial determinant for graft suitability and ideal ratios of 0.8-1 have been advocated. Many centers now have experience with small for size grafts and it is acceptable for the GRWR to be as low as 0.5-0.6 if there are accompanying factors of portal vein pressure ≤15 mmHg, middle hepatic vein reconstruction, or young donor age [17]. On the other hand, large for size grafts are problematic in small infants due to compromised portal venous flow and small abdominal cavity. Use of reduced mono/bi-segment grafts and delayed abdominal closure using mesh/skin closure help circumvent abdominal compartment syndrome [16]. Thus, babies as small as 4-5 kg are now being routinely transplanted at select centers in India.

Other marginal grafts are increasingly being accepted. These include older donors in the absence of size mismatch and severe steatosis, moderately steatotic liver grafts if predominant pattern is of microsteatosis instead of macrosteatosis, donors with a BMI ≥30 kg/m^2 and HBsAg-negative/HBcAb-positive liver grafts in HBsAg negative recipients with active immunization and post-transplant antiviral prophylaxis to prevent *de novo* HBV infection [17]. These strategies have considerably increased the donor pool for liver transplant in scenarios hitherto found unsuitable.

PERSISTING CONCERNS

Studies on long term morbidities, effects of immunosuppression and quality of life post liver transplant are lacking from our country. LT requires lower immunosuppression compared to other organs. Indian patients have been shown to do well on lower immunosuppression as infections are more common in our scenario [4,5]. Regimens vary across different programs but corticosteroids remain the induction agents of choice with dual agent regimens including calcineurin inhibitors and renal sparing mycophenolate for the first year, with the aim to come down to a single agent by the second year. The desired ideal outcome is attainment of prope tolerance, *i.e.*, almost immune tolerant state where the recipient is alive with first allograft with no ongoing rejection episode on tacrolimus therapy with trough levels less than 3 ng/mL, three years post LT. Studies indicate that almost 20% pediatric patients may attain such immune tolerance with maximal chances for those transplanted in infancy [18]. However, the SPLIT database analysis has revealed that the ideal triad of normal growth, stable allograft function on single-agent immunosuppression, and an absence of immunosuppression-related complications is achieved in only about a third of recipients 10 years after LT [1]. Steroid free protocols using antibody induction (ATG/basiliximab) along with tacrolimus are not yet in vogue but steroid-free tacrolimus-based immunosuppression may result in an enhancement of graft acceptance in the long term as well as in a higher proportion of children becoming prope tolerant [19,20].

Lack of a database greatly inhibits accurate analysis of trends, outcomes and long term results. Non-availability of long term followup from many recipients from overseas is another disadvantage. With the formation of the Liver Transplant Society of India, efforts are on for a national registry, hopefully more data should be available in the coming years. Low numbers for DDLT, especially in Northern India, is amongst the foremost immediate concern that requires intense campaigning and education to change the social mindset. Encouraging organ donation is the need of the hour.

CHANGING SOCIAL SCENARIO

Perhaps, the most crucial limiting factor in our country has been the cost of liver transplant. The programs are largely driven through the private sector, and health care insurance is still not widely prevalent in our country. Moreover, most insurance companies do not provide cover for diseases of perinatal onset or genetic etiology. The advent of crowd funding platforms where strangers come together on the internet to fund a medical catastrophe for an unknown person is heart-warming and provides an insight into the social responsibility the community is prompt to take up when transparency is assured. These campaigns run on social media with tight timelines ranging from a week to a month, and at times funds have been raised in a day or two for emergency transplants. Crowd funding with the support of few philantrophic organizations and individuals dedicated to funding liver transplants has thus made transplantation attainable for those with limited resources. Crowd funding works best for children awaiting transplants, perhaps due to the emotive pull of images and videos of innocent children struggling to wade off certain death that a transplant could prevent. The predicament of the parents, one of whom is the organ donor most of the time, also touches a cord. With this active support of the community in facilitating transplants for children, liver transplant seems to have finally come of age in our country.

FUTURE DIRECTIONS

High-resolution sequence mapping of DNA variation is now feasible and liver tissue transcriptional signatures are being studied to identify candidates likely to achieve tolerance and withdrawal of immune suppression. Genome wide association studies or NGS for cytokine genotyping to detect single nucleotide polymorphisms in cytokine gene promotor regions may help identify recipients at low risk for rejection.

Meanwhile, expansion of this facility in the public sector is needed as liver transplant is still not available routinely to those with limited resources. We wait to realize the dream of DDLT becoming the primary modality, as it is in the Western countries, by concerted efforts to promote organ donation.

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