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Biliary Atresia-Challenges of Liver Transplantation

Case Report

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Abstract

Objective: Biliary Atresia is a rare condition in early infancy in India, as nearly 2500-5000 such children are born each year. Liver transplantation is a highly successful treatment for biliary atresia, as survival after surgery has increased dramatically in recent years. However, the poor awareness about needs and urgency for liver transplantation for young infants born with Biliary Atresia, availability of donors and lack of facilities for transplantation surgeries, and socioeconomic inequities in accessing the service across the world including advanced countries like USA and UK lead to children experiencing long waiting times for procedure. The objective of this publication of clinical cases is to describe epidemiological risk factor; ordeals of liver transplantation in India and raising an alert for better preparedness of the health system and other stakeholders.

Location: Case reports of two liver transplants in Mumbai and Bengaluru in August 2022.

Participants: In this review 2 liver transplant surgeries one each in Mumbai and Bengaluru, India in August 2022 are discussed to drive the need for a comprehensive effort from the Government, families and the health insurance companies. The first case was of an infant of 9 months old boy, who underwent within two weeks of birth a corrective surgery (Kasai procedure) to allow for bile drainage, but the surgery failed and resulted in decompensated chronic liver disease with jaundice and other complications needing liver transplantation. He had to undergo an incompatible liver transplant with an aunt's donated liver as parents were unsuitable. The second case was of a 11-month-old boy needing primary liver transplant due delayed manifestation (at 6 months), diagnosis and mobilizing resources.

Measurements: The operating procedures and the outcome in the first month. The financing mechanism for the procedure and limitation of country's health assurance scheme.

Results: The immediate outcome of both the liver transplants were encouraging.

Conclusion: liver transplantation for Infants with Biliary Atresia is an urgency, but as of now must wait for long. families, government, insurance companies and even the facilities and surgeons need to join hands for this arduous process. Unless exceptional attention is granted it is difficult to save the children.

Materials & Methods: Reports on the ordeals of two cases of Liver transplants one in Bengaluru and another in Mumbai, India in August 2022.

Key Words: Bile Duct; Biliary Atresia; Liver Transplantation; Porto-Enterostomy; Ayushman Bharat; State Health Assurance Schemes.

Introduction

Biliary Atresia is poor development of the bile duct and is progressive in nature. Globally one in 15,000 births suffer with this condition. Most affected children will eventually develop end-stage liver disease and require liver transplantation. Bile entry into the intestines can be re-established from the liver to the intestine by joining the two directly. The surgery must be done before all the intrahepatic bile ducts leading to the porta hepatis are destroyed. It is illness needing surgical intervention called 'Kasai procedure' named after its inventor a Japanese surgeon. If the diagnosis is delayed liver transplantation is the only option.

Children with biliary atresia often experience long wait times for transplant, across the world including advanced countries like USA and UK due to family's preparedness or even lack of the facilities except in a few metropolitan cities. The insurance system of a country also delays the process.

A liver transplantation is a surgical procedure in which a liver functions are damaged beyond the body's capacity to regenerate is removed and replaced with a healthy liver. A whole liver may be transplanted, or just part of one. In most cases the healthy liver will come from an organ donor who has just died. Sometimes a healthy living person usually a family member will donate part of their liver. A patient undergoes a liver transplant when his/her liver fails to function normally, due to chronic liver failure. Chronic liver failure occurs over months and years in a patient. The most common cause for chronic liver failure is cirrhosis, in which the normal tissues of a liver get scarred resulting in failure of the organ. Major causes of cirrhosis in India are Hepatitis A & B infections, alcoholic diseases due to excessive alcohol consumption, and Non-alcoholic fatty liver disease, a condition in which fat builds up in the liver, causing inflammation or liver cell damage. In India Liver cirrhosis is the most common reason for a liver transplant.

The first ever effort to replace a human liver was made at the University of Colorado on March 1, 1963. That patient died as did four others during the next 7 months. Dr Starzl is credited with performing the first successful liver transplant, on May 5, 1963, in USA [1,2]. Professor Roy Caine performed the UK's first liver transplant at Addenbrooke's hospital in Cambridge 1968 [3]. Sir Terence is credited with first transplant with long-term success on 18th August 1979, in United Kingdom. In India the first unsuccessful deceased donor liver transplant (DDLT) was done in 1995 followed by a few more unsuccessful attempts. The first successful DDLT and the first successful Living donor liver transplant (LDLT-November) were done in 1998 by Prof. Rajasekar. Entire world is seeing a leap and bund improvement in Liver transplantations in the last 9 years. Currently more than 1800 liver transplants (LT) are, performed in 90-100 active LT centres in India annually. A Liver Transplant Registry (ILTR, www.iltr.org) is established in August 2019 and prospective data about the number of liver transplantations done in the country is available since then.

Bile is a digestive juice secreted from the liver it enters the intestine through a bile duct. It facilitates the digestion of fat and absorption of fat-soluble vitamins we consume. Incomplete development of the bile duct is called Biliary Atresia. This leads to cholestatic or direct jaundice and liver damage. Though exact cause is not known, theories of viral, toxin or genetically related damage to the biliary pathways are considered. As it is not an inheritable condition parents need not worry if one baby suffers from Biliary Atresia, other siblings will not suffer from the same. Babies with Biliary Atresia look normal at birth and grow well initially. Jaundice is the first symptom, appearing any time after birth to eight weeks of age, usually observed when stool appears pale or white due to lack of bile pigment. Urine is dark yellow and stains the diaper or nappy yellow as against normal colourless, non-staining urine till 3 months of age. As the disease advances abdomen bloats due to increased size of liver and spleen. Rarely there can be bleeding from the nose or umbilical cord. BA is the most common reason for liver transplants among children and the only hope for children born with BA.

Biliary atresia (BA) is a rare disorder with a higher incidence among girl babies. Its incidence is approximately 1 in 10,000 to 15,000 births in the United States and 1 in 10,000 to 20,000 live births in India.

In this review 2 rare liver transplant surgeries one each in Mumbai and Bengaluru, India in August 2022. The first case was of an infant who underwent within two weeks of birth a corrective surgery (Kasai procedure) to allow for bile drainage, but the surgery failed and resulted in decompensated chronic liver disease with jaundice and other complications needing liver transplantation and underwent a liver transplant in 9th month of age. This was a rare but successful incompatible Living Donor Liver Transplant done on 18 August 2022. The second case was of a 11-month-old boy needing primary liver transplant due delayed manifestation (at 6 months), diagnosis and mobilizing resources. This case demonstrates how the health system failed in supporting the family, because of state specific health assurance schemes and not acknowledge in other province of the same country.

Case Reports

1. **Incompatible Living Donor Liver Transplant:** The infant, Vayu, a nine-month-old boy has undergone an incompatible liver transplant at Mumbai's Nanavati Hospital in early August 2022. He was diagnosed with Biliary Atresia, on the sixth day after birth. Despite a corrective hepatoportoenterostomy in the second week to allow bile drainage, he developed decompensated chronic liver disease with complications. While Vayu's parents were unsuitable for liver donation, his aunt volunteered to donate a part of her organ [8]. During the pre-surgical work-up, another major hurdle sprang up for the team when Vayu developed antibodies against blood group A, that were found to be high at just nine months increasing the chances of rejection of the organ. To combat the rejection Vayu was given Rituximab (antibody against CD20 cells responsible for this antibody production) and followed by a plasma exchange session to remove the preformed antibody. The team had planned an ABO incompatible liver transplant as Aunt's blood group is A +ve, while that of Vayu's is O +ve. In a rare surgery, first his blood was desensitised to remove the antibodies to avoid his body rejecting the transplanted organ. A day before his planned transplant surgery, CT (Computerised tomography) scan of chest for Vayu showed suspicion of pneumonia (lung infection) again that was treated and thus after several hurdles, a successful incompatible Living Donor Liver Transplant was done on August 18. "In medical literature, only five such incidents have been r After the

procedure the baby was shifted to paediatric intensive care unit and given antibiotics, IV fluids, kept on nil by mouth. The mother was advised to keep expressing her breast milk and 2 days after the surgery the expressed mother milk was fed through a Ryle's feeding tube and monitored. Once he tolerated the feeds and child's condition was stable, he was shifted to a single room ward on day 5. This boy was discharged after 3 weeks from the hospital, starting the supportive management of jaundice that includes

- **Nutrition:** As the caloric requirement is 1.5 times of the normal requirement Smyl MCT (medium chain triglycerides) oil was added to the milk. The protein intake was adjusted at 4 gm/kg/day and Fat-soluble vitamins A, D E and K were supplemented. B complex vitamins was given 2-3 times of the daily allowance.
- **Prevention and management of infections:** A long-acting antibiotics (Amoxicillin) was given.
- **Choleretics:** Urso deoxycholic Acid (UDCA) a drug which makes the bile to flow easily was used in the dose of 15-30 mg/kg/day in 2 divided doses.
- Regular follow up and monitoring and Vaccination as per national schedule recorded across the globe [8].

2. **Primary Liver Transplant due to Delayed diagnosis and ordeal of resource mobilization:** Manipal Hospital in Whitefield Bengaluru reported of a child of 11 months operated for BA on 23 August 2022. The baby had developed symptoms of jaundice, yellow eyes, and pale stools at the age of 6 months. The first consultation in Hooghly, West Bengal had discouraged the parents saying the baby will not survive. On second consultation in Kolkata, they referred the case to Bengaluru. The father's for donating a portion of his liver and baby for transplantation lasted 8 and 12 hours respectively. A long-acting antibiotics (Amoxicillin) and UDCA was given in the dose of 15-30 mg/kg/day in 2 divided doses. Hospital discharged father in 10 days and the baby after 3 weeks and both are doing well now. The father has recovered fully and the boy recouping [9].

The pity is the family had parent state West Bengal's Health assurance card that was not valid in the hospital, but they did not have the much-advertised Ayushman Bharata (AB) card valid across the country. The father had to spend 1.5 million Indian Rupees (20,000 US$). By selling some land, donate a part of his own liver and go through the ordeal in an alien state. This calls for universalizing the AB Card or amutual agreement among the provincial governments to respect state specific health assurance cards and stand guarantee for the payments.

Discussions

Biliary atresia is a poor development of the bile duct and is progressive in nature. Usually identified in neonatal or early infancy, and its aetiology is not fully understood yet. Generally, there is delay in identifying most affected children, eventually leading to development of end-stage liver disease and require liver transplantation. As diagnostic and management facilities are available only in metro cities in India, most cases remain untreated by hepatoportoenterostomy, and progress to end stage liver failure and death. It is a surgical emergency in a new-born. Any baby with jaundice beyond 2 weeks of life, the parents need to get the baby evaluated.

1. **Pathophysiology**: Absence or poor development or blockade of Biliary duct that connects the liver and the small intestine is known as Biliary Atresia and an uncommon but serious condition. Early surgical intervention is the only way out to avoid irreversible liver damage. Portoenterostomy treatment for biliary atresia in India is revolutionary and one-of-a-kind and produces excellent results and liver transplantation, have given good lease of life to children for long term survival. Bile entry into the intestines can be restored before all the intrahepatic bile ducts leading to the porta-hepatis are destroyed, most popular procedure is known as Kasai Porto-enterostomy after its inventor a Japanese Surgeon. The results of the surgery performed within 2 months of birth are reported to be satisfactory. In later months liver transplantation (LT) is the only option. The indications of LT are failure of the Kasai procedure, Poor growth due to Cholestasis, portal hypertension not responding to endoscopic management, upper intestinal bleeding occurring repeatedly, Ascites that compromises the functions of the lung, bowel, or kidney due to pressure on the respective organs, Hepatopulmonary syndrome, Progressive liver dysfunction and Cholestasis. The potential risk of transplant versus the survival benefit at any given stage of disease determine the timing of liver transplantation. These children often experience long waiting times for liver transplant and deserve exceptional priority due to the severity of disease. Family's preparedness in terms of resources and willing member to donate a portion of liver and matching of the blood groups etc. are critical causes of the delay in liver transplantation [12]. The results of treatment of biliary atresia in India compared to the developed nations like USA and UK fall short [11].
2. **Burden of the condition in India:** With a midyear population of India of 1,417,173,173, (a 0.68% increase from 2021), we will have 24.6 million children born this year and by 2023 we will reach an annual birth of 25 million. Given an estimated incidence rate of 1 child born with Biliary Atresia for every 10,000 to 20,000 live births we will have about 2500-5000 new-borns with BA.

Diagnosis

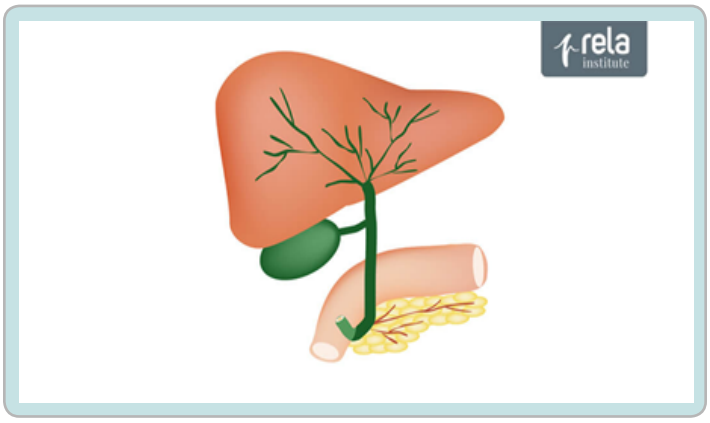
Biliary Atresia is suspected when there is jaundice occurs after 2 weeks of birth and then the diagnosis is made based on 3 tests.

1. There is increase in the blood level of direct bilirubin with markedly raised is GGTP and little increase in liver enzymes SGPT, SGOT.
2. **Ultrasonography (**USG) abdomen showing either absent gall bladder or abnormal shape or small size and invisible Common bile duct.
3. **HIDA scan:** Hepatobiliary iminodiacetic acid scan **(HIDA)** a nuclear imaging scan that shows dye uptake by liver as normal, but the dye is not seen in the intestine. Biliary Atresia is ruled out if HIDA is normal.
4. **Liver biopsy:** liver biopsy done before surgical intervention or during surgery. An experienced pathologist only can confidently diagnose Biliary Atresia.

The Surgery

1. **Kasai procedure:** The preferred and first choice for biliary

atresia treatment is Kasai procedure (also called a Roux-en-Y) that helps re-establish bile flow from the liver to the intestine by joining the two directly. Surgeons remove the diseased or damaged bile ducts outside the liver. They use a small segment of the patient's own intestine to replace the ducts at the spot where bile is expected to drain, connects to the liver and the other end connects to the rest of the intestine. Both bile flow and liver function will be restored to normalcy in at least 1/3 of children undergoing this procedure, may not need liver transplantation. The other 2/3 who undergo the Kasai procedure will not have sufficient bile flow and liver function and Half of them will need to liver transplantation after the Kasai procedure while the other half will need to have it at some later date in their lifetime.



2. **Liver Transplantation:** The four main stages of liver transplantation include: the donor hepatectomy-cutting the portion to be transplanted, the recipient hepatectomy-consists of removing the damaged liver or a portion of it, the implantation of the graft (4 vascular anastomoses), followed by haemostasis and the bile duct reconstruction. The liver transplantation involves

- Screening of both donor and the recipient through a series of tests to ascertain the benefits and the potential risk involved. Matching criteria for the donor include age, blood type, organ size, etc.
- During the transplantation procedure the surgeon cuts open the abdomen and removes the unhealthy or dead liver from the recipient's body and then implants the new liver from the donor kept ready by taking it out from a donor or dead person and then all the blood vessels and the bile ducts are connected to the new liver inside the recipient's body. The transplanted portion of the liver in the patient's body regrows in a few months.
- For first few days the patent is kept in intensive care unit (ICU) and then the patient is shifted to a regular ward for 3-4 days and monitored for the progress before discharging. Two weeks after the discharge a follow-up visit is asked, and subsequent follow-ups will be at intervals of six to nine months to monitor normal functioning of the liver and bile.

The basic risks involved in liver transplantation include:

a. **Rejection:** The chances of the patient's immune system attacking the newly transplanted liver inside the body and rejecting it are high around 60. Anti-rejection medicines are prescribed to patients after a liver transplant.

b. Infection-As the anti-rejection medicines given may lead to the weakening of the immune system and as a result, the patient becomes more prone to external infections.

c. Liver function problems-Sometimes the implanted liver doesn't function normally as it should in around 1-5% of patients, and in such cases, a second transplant may be required.

Prognosis

The success rate is reported to be 80-90% if the surgery is done within 6 weeks of birth. A delay up to 6 to 12 weeks, results in the success rate dropping down to 50-80%. Beyond 12 weeks the success rate is minimal. Establishment of bile drainage is an indication of the success of Kasai procedure, even though slow liver damage continues and many of the patients ultimately require liver transplantation. According to a recent study, if surgery is done within 30 days the chance of survival with patients own liver is 50% at 4 years. Between 30-90 days, the chance of survival is 36% at 4 years [7]. If surgery is done after 90 days, most of the patients will require liver transplant within first year of life. Hence early diagnosis is a key factor.

A retrospective study of 3,438 transplant candidates with biliary atresia undergoing liver transplantation, 15% were of primary transplantation, 17% for salvage transplants after early and 67% after late Kasai failure. Children with late Kasai failure had to wait significantly longer periods and post-transplant graft survival was poor in comparison to those that did not undergo Kasai hepatoportoenterostomy and were taken for primary liver transplantation. Candidates undergoing primary liver transplantation or salvage transplantation after early Kasai failure had equivalent waiting period and post-transplant survival outcomes [11]. This review infers that Kasai hepatoportoenterostomy should be the standard of care in biliary atresia, as a delay will lead to the need for liver transplant beyond the first year of life. It does not jeopardize subsequent transplant outcomes, even with early failure.

Liver Transplantation in India

India is to celebrate silver jubilee year in 2023 as it was only in 1998 that the first successful deceased donor liver transplant (DDLT) and a living donor LT (LDLT) were performed in India. The National Organ and Tissue Transplant Organisation (NOTTO) is a regulatory body that functions as an apex Center for all procurement and distribution of Organs and Tissues in the country. The Liver Transplant Society of India (LTSI) is trying its best to encourage every active centre to contribute data in the ILTR. Current data shows significant regional variations in the country. At present data shows that most recipients are males (80%), and that too adults (85%). In India DDLT is predominant, LDLT is most performed in India, (around 85% of cases) as compared to DDLT in the western world [1]. Globally it is recorded that recipients have lived a normal life over 30 years after the operation. The Indian Liver Transplant Registry (ILTR, www.iltr.org) is accruing prospective data from August 2019 only. While Kidney transplantation are the first with annual number in the range of 7500 (2021) as against a requirement of 220,000, persons with

renal failure, liver transplants are the second most common type of transplant surgery in India after kidney transplants. 9,236 liver transplants were done in USA during 2021 [2]. Liver transplant accounted for 22% of the 41,354 transplants performed in 2021 in USA. In United Kingdom during 2020/21, 606 liver transplants were carried out, followed by 71 in Scotland.

Whereas an estimated 20,000 people requiring liver transplant in India annually, only around 2000 (10%) liver transplants (LT) are performed annually, in 90-100 active LT centres. The Indian Liver Transplant Registry (ILTR, www.iltr.org) is now established and accruing prospective data from August 2019. Around 90% of patients survive one-year post-surgery. The long-term success rate is 55-60% and most patients lead a normal and healthy life post-transplant but must take lifelong medications and make some major lifestyle changes.

A study of the clinical, biochemical profile and outcome of 20 patients with biliary atresia (BA) who underwent living related liver transplantation (LRLT) in a private hospital in New Delhi during 2008-2013, found that 18 patients with BA with a failed Kasai procedure and 2 without a prior Kasai's portoenterostomy received a liver transplant. At a median follow up of 2 y and 6 months, both the patient and graft survival rates were 90 %. The median age of the recipients at the time of LRLT was 8 months and 12 (60 %) of the transplanted children were less than or equal to 1 y of age. The male-female ratio was 1.8:1. The median weight was 7.3 kg (5.8-48 kg); two thirds were less than 10 kg. The median pre-transplant total serum bilirubin (TSB) and international normalized ratio (INR) were 12.98 (0.5-48.3) mg/dl and 1.3 (1.0-3.9) respectively. All patients received a living related graft and there was no donor mortality. The median duration of postoperative ventilation was 14 h. The post-operative complications were infection (30 %), vascular complications (20 %) and acute rejection (20 %). The median duration of postoperative hospital stay was 21 d (17-42). Two patients died of combined hepatic and portal vein thrombosis in the early postoperative period [13].

Conclusion

- Biliary Atresia is not uncommon in India as an estimated 2500-5000 children are born every year, it is the major reason for Primary Liver transplantation among infants in India.
- Biliary Atresia is suspected when 1) there is increase in the blood level of direct bilirubin with markedly raised is GGTP and little increase in liver enzymes SGPT, SGOT, to be confirmed by ultrasonography.
- Children with biliary atresia often experience long wait times for transplant as the Families preparedness for this arduous surgery is limited.
- Delay in diagnosis and doing portoenterostomy may lead to the need for primary liver transplantation, facilities for which are available in major metropolitan cities only.
- Since it is rare opportunity for the surgeons, to venture such a surgery, they and the hospitals should give maximum possible concession in expenses.
- The presentation of 2 rare cases of Liver transplantation in infants is to acknowledge and create an awareness about an important topic of Biliary Atresia in India, and to alert the health system, parents, and health insurance schemes to gear up to address the challenge.

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