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Literature Review

Biliary Atresia - Challenges of Liver Transplantation - in Young Infants

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Abstract

Biliary atresia is a progressive, fibro-obliterative disorder of the intra and extrahepatic bile ducts among new-borns. Globally one in 15,000 births suffer with this condition. In India with an annual birth of 25 millions, we expect from 2500 - 5000 births with this defect annually. Bile drainage can be restored by Kasai Porto-enterostomy, if the surgery is done before all the intrahepatic bile ducts leading to the porta hepatis are destroyed. If the diagnosis is delayed to later months, primary liver transplantation is the only option to save the affected babies. Most affected children will eventually develop end-stage liver disease and require liver transplantation. Children with biliary atresia often experience long wait times for transplant, across the world including 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.

The objective of this article is to alert the community and the health system to rise above petty administrative issues of jurisdictions and provide unconditional services the new-borns with Biliary Atresia deserve. The author presents in this article two case reports of August 2022 in India, first case wherein liver transplantation was required due to failure of the initial Kasai hepato-porto-enterostomy failed and the second case in which primary liver transplantation was required due to delayed diagnosis, and the hardship family had gone through due to non-transferable inter-state health assurance scheme, drawing attention of the Governments for mitigation.

Apart from 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 these children.

Reports on the ordeals of two cases of Liver transplants one in Bengaluru and another in Mumbai in August 2022 in India, Review of the literature and the struggle of the families in mobilizing the resources and accessing the services.

Introduction

A liver transplant is a surgical procedure during which a non-functional liver is removed and replaced with a healthy liver from a deceased donor or from a living donor. 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 and 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.

Biliary atresia is the most common reason for liver transplants among children. Bile is a digestive juice secreted from the liver and is very important for the digestion of fat in food and for absorption of fat-soluble vitamins. Bile passes into the intestine through a bile duct. Poor development of the bile duct is called Biliary Atresia. It is a genetic disease affecting the liver, leading to cholestatic jaundice or liver damage. Though exact cause is not known, theories of viral, toxin or genetically related damage to the biliary pathways are considered Pathology includes hemochromatosis, which causes excessive iron build-up in the liver, and Wilson's disease, which causes excessive copper build-up in the liver. Liver transplantation is the only hope for children born with BA.

Though exact cause is not known, theories of viral, toxin or genetically related damage to the biliary pathways are considered. It is not an inheritable condition; therefore, parents need not worry that if one baby suffers from Biliary Atresia then other siblings may also suffer from the same disease. Babies with Biliary Atresia are normal at birth and grow well initially. Jaundice is the first sign, appearing from birth to eight weeks of age. It is noticed when stool appears pale or white as there is no bile pigment. Urine is dark yellow and stain the diaper or nappy yellow instead of normal new-born's colourless water like urine till 3 months of age. In later stages abdomen looks full due to increased size of liver and spleen. Occasionally bleeding can occur from the nose or umbilical cord.

Biliary atresia (BA) is a rare disorder with a slight increased frequency in females. 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.

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 performed the UK's first transplant with long-term success on August 18, 1979. The first deceased donor liver transplant (DDLT) in India was done in 1995 but it was unsuccessful, followed by a few unsuccessful attempts. The first successful DDLT in 1998 and shortly thereafter by the first successful Living donor liver transplant (LDLT) in November 1998 both performed by Prof. Rajasekar. Entire world is seeing a leap and bund improvement in Liver transplantations in the last 9 years. Setting a sort of records. More than 1800 liver transplants (LT) are performed in India 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.

Case Reports:

1. The infant, Vayu, a nine-month-old boy has recently undergone an incompatible liver transplant at Mumbai's Nanavati Hospital. He was diagnosed with Biliary Atresia, at birth when he was only six days old. Within two weeks, he underwent a corrective surgery called Kasai hepatoportoenterostomy to allow for bile drainage. However, the surgery failed so he developed decompensated chronic liver disease with jaundice and other complications. Since liver transplant was the only permanent solution to save Vayu's life, his family opted for it. While Vayu's parents were unsuitable for liver donation, his aunt volunteered to donate a part of her organ.

   During the pre-surgical work-up, another major hurdle sprang up for the team when Vayu's Anti A antibody titres were found to be high, and he had developed antibodies against blood group A. "All children develop antibodies after the age of two years, but Vayu's Anti A antibody titres were found to be high at just nine months. This further increased the chance of rejection of the organ.

In preparation for the incompatible liver transplant, Vayu received Rituximab (antibody against CD20 cells responsible for this antibody production) and then a session of plasma exchange to remove the preformed antibody. The team planned an ABO incompatible liver transplant as Vidhi's blood group is A +ve blood group 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 scan of chest for Vayu showed suspicion of pneumonia (lung infection) again. However, after several hurdles, Vayu underwent a successful incompatible Living Donor Liver Transplant 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 is asked to keep expressing her breast milk. After 2 days the expressed mother milk is introduced through a feeding tube and monitor his abdomen. Once he tolerates feeds and is stable, 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: 1) Nutrition: As the caloric requirement is 1.5 times of the normal requirement Smyl MCT oil was added to the milk. The protein intake was 3 - 4 gm/kg/day. Fat soluble vitamins like A, D E and K need were supplemented. B complex vitamins need to be given 2-3 times of the daily allowance. 2) Prevention and management of infections: A long-acting antibiotics (Amoxicillin) was given. 3) Choleretics: These are the drug which makes the bile to flow easily. Urso deoxycholic Acid (UDCA) is used in the dose of 15-30 mg/kg/day in 2 divided doses. 4) Regular follow up and monitoring and Vaccination as per national schedule recorded across the globe.

2. 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 Choleretic Urso deoxycholic Acid (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 [7].

   In this case more than the surgery, it's cost and hardship the family had to undergo, the author's keen interest to draw attention to a systemic challenge that need to be addressed. The family had parent state West Bengal's Health assurance card that was not valid in the hospital in another state of the same country, Instead, if the there was one Ayushman Bharata card valid across the country the hardship could have been avoided. The father had to spend 1.5 million Indian Rupees (20,000 US$). By selling some land, apart from donating a part of his own liver and go through the ordeal in an alien state. This calls for universalizing the AB Card or a mutual agreement among the provincial governments to respect state specific health assurance cards and stand guarantee for the payments.

Discussions

Biliary atresia is a progressive, fibro-obliterative disorder of the intra and extrahepatic bile ducts in infancy of unknown ethology. Most affected children will eventually develop end-stage liver disease and require liver transplantation. If untreated it has a progressive course 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, parents must get the baby evaluated.

Pathophysiology: Biliary atresia is a rare condition in new-born infants in which the common bile duct between the liver and the small intestine is blocked or absent. Early surgical intervention to treat biliary atresia is critical to prevent irreversible liver damage. With the advent of portoenterostomy and liver transplantation, children have a promise for long term survival. Kasai procedure named after its inventor Japanese surgeon is the treatment of choice. Bile drainage can be restored by Kasai Porto-enterostomy, if done before all the intrahepatic bile ducts leading to the porta-hepatis are destroyed. Best results are seen if the surgery is performed within 60 days of birth.

In later months liver transplantation (LT) is the only option. The indications of LT are Primary failure (lack of bile drainage) after the Kasai procedure, Poor growth despite all measures, due to Cholestasis, Complications of portal hypertension not responding to endoscopic management, repeated upper intestinal bleeding, Refractory Ascites that compromises lung, bowel, or kidney function, Hepatopulmonary syndrome, Progressive liver dysfunction and Progressive Cholestasis.

The timing of transplant for biliary atresia requires careful consideration of the potential risk of transplant versus the survival benefit at any given stage of disease. Children with biliary atresia often experience long wait times for transplant unless exception points are granted to reflect severity of disease. Family preparedness for this arduous process is therefore critical [11]. The results of treatment of biliary atresia in the developed nations have not been achieved in India [10].

Burden of the condition in India: With a midyear population of India of 1,417,173,173, (a 0.68% increase from 2021), in 2022 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 1) there is increase in the blood level of direct bilirubin with markedly raised is GGTP and little increase in liver enzymes SGPT, SGOT. A combination of 3 tests confirms the diagnosis. 2) Ultrasonography (USG) abdomen shows gall bladder is either absent or abnormal shape or small size. Common bile duct is not seen. 3) HIDA scan: Hepatobiliary iminodiacetic acid scan) is a nuclear imaging scan done by injecting a dye. While normal liver takes up the dye and excrete into the intestine, in Biliary Atresia, liver uptake is usually normal, but the dye does not pass into the intestine. If HIDA scan is normal, Biliary Atresia is ruled out. 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 biliary atresia treatment is called 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 begin the procedure, by removing 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. This segment not only connects to the liver, but also connects to the rest of the intestine.

2. **Liver transplantation:** The complete transplant procedure is composed of four main stages: the donor hepatectomy, the recipient hepatectomy, the implantation of the graft (4 vascular anastomoses), followed by haemostasis and the bile duct reconstruction. The liver transplantation involves i) Screening of both donor and the recipient through a series of tests to risks involved. ascertain the benefits and the potential risk involved.

Matching for LT

i) Matching criteria for the donor with the recipient are based on age, blood type, organ size, etc. ii) During the transplantation procedure the surgeon removes the unhealthy or dead liver from the recipient's body and implants the new liver from the donor after making an incision in the abdomen. Then all the blood vessels and the bile ducts are connected to the new liver inside the recipient's body. The new portion of liver in the patient's body starts to regrow at its normal rate in a few months. iii) The discharge process starts once the patient is shifted to a regular ward from an ICU after the transplant. The first appointment after the transplant is usually scheduled after two weeks of discharge. Later, regular follow-ups will be at intervals of six to nine months to ensure there are no complications.

The basic risks involved in liver transplantation include 1) 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. 2. 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. 3. 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

If the surgery is done within 6 weeks of birth the success rate is 80 - 90%. If done between 6 to 12 weeks, the success rate drops down to 50 - 80%. Beyond 12 weeks the success rate is minimal. The success in Kasai procedure means that the bile drainage is established. But despite adequate drainage progressive slow liver damage continues. Many of the patients will ultimately require liver transplantation. According to a 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. If surgery is done after 90 days, then most of the patients will require liver transplant within first year of life. Hence early diagnosis is a key factor.

Liver transplantation in India

India is to celebrate silver jubilee year soon 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 NOTTO (National Organ and Tissue Transplant Organisation) is a regulatory body deemed to function as an apex Center for all India activities of coordination and networking for procurement and distribution of Organs and Tissues in the country. Although there is no law or directive yet making it compulsory for all centres to contribute data in the ILTR, the Liver Transplant Society of India (LTSI) is trying its best to encourage every active centre to do so. Significant regional variations exist, but most recipients are males (80%), and most are adults (85%). Unlike in the Western world, where DDLT is predominant, LDLT is most performed in India, (around 85% of cases) [1]. Globally recipients have been known to live a normal life over 30 years after the operation. The Indian Liver Transplant Registry (ILTR, www.iltr.org) is now established and accruing prospective data from August 2019 only. liver transplants are the second most common type of transplant surgery 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 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 2y 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 1y 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 14h. The post-operative complications were infection (30%), vascular complications (20%) and acute rejection (20%). The median duration of postoperative hospital stay was 21d (17 - 42). Two patients died of combined hepatic and portal vein thrombosis in the early postoperative period [13].

A study of 3,438 transplant candidates with biliary atresia listed for liver transplantation, 15% were listed for primary transplantation, 17% for salvage transplant after early Kasai failure and 67% after late Kasai failure. Children with late Kasai failure had significantly supe-

rior waiting list and post-transplant graft survival in comparison to those that did not undergo Kasai hepatoportoenterostomy and were listed for primary liver transplantation. Candidates listed for primary liver transplantation and for salvage transplantation after early Kasai failure had equivalent waiting list and post-transplant survival outcomes [10]. The review infers that Kasai hepatoportoenterostomy should remain the standard of care in biliary atresia. Any delay will lead to the need for liver transplant beyond the first year of life in a subset of recipients and does not jeopardize subsequent transplant outcomes, even with early failure.

Summary

- 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 there is an increase in the blood level of direct bilirubin with markedly raised is GGTP and little increase in liver enzymes SGPT, SGOT and confirmed by ultrasonography.
- Children with biliary atresia often experience long wait times for transplant as the Families preparedness for this arduous process 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.
- The cost is prohibitive for many average Indian families and demands an urgent consideration by the national and provincial governments to include in Ayushman Bharat Scheme, irrespective which state the baby belongs.
- Since it is rare opportunity for the surgeons, to venture such a surgery, they and the hospitals should give maximum possible concession charging only the actual expenses.

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