REVIEW ARTICLE

Recent Trends in the Diagnosis and Management of Biliary Atresia in Developing Countries

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Need and purpose of review: Biliary atresia is a progressive obstructive cholangiopathy and is fatal if left untreated within 2 years of life. Delay in referral is because of difficulties in differentiating it from physiologic jaundice and identifying an abnormal stool color. This paper presents an overview on the diagnosis and discusses the current strategies in the management of this disease in developing countries.

Methods: Articles were retrieved from the PubMed database using the terms 'biliary atresia', 'Kasai portoenterostomy' and 'pediatric liver transplantation'. Contents of the article are also based on personal experience of the authors.

Conclusion: A national screening program using stool color cards as part of standard care in the neonatal period will greatly improve early detection of biliary atresia. Outcomes will improve if it is diagnosed at the earliest after birth, the child is referred to an experienced pediatric hepatobiliary unit for evaluation, and undergoes an early Kasai procedure. If an early Kasai portoenterostomy is performed, nearly half of all children survive into adolescence, and about one-third are likely to have a long-term, symptom-free life with normal liver biochemistry. Sequential treatment combining Kasai as first line and liver transplantation as second line results in 90% survival for children with biliary atresia.

Keywords: *Biliary atresia, Kasai portoenterostomy, Liver transplantation, Neonatal cholestasis.*

Biliary atresia (BA) is a progressive obstructive cholangiopathy of both the intra- and extra-hepatic biliary tree, leading to cholestasis and cirrhosis. It usually manifests in the first few months of life with jaundice, pale stools, high colored urine and hepatomegaly. The etiopathogenesis of BA is multifactorial, and its incidence has been reported to vary from 1:9000 to 1:15000 [1,2]. It is fatal if left untreated in first 2 years of life.

DIAGNOSIS OF BILIARY ATRESIA

BA must be suspected in all neonates in whom jaundice persists after the period of physiologic hyper-bilirubinemia (first 14 days of life). Jaundice is the only symptom of BA in the neonatal age group. The diagnosis is delayed because of failure to differentiate jaundice due to liver disease from physiologic jaundice. Delay in diagnosis is unfortunate since treatment is most effective in this age group (before 30 days of life). Two distinct types of BA have been identified – the embryonic or syndromic type, where associated extrahepatic malformations are present and there is no jaundice-free interval; and the perinatal or isolated type, where there may be a jaundice-free interval [3]. Extrahepatic malformations or Biliary Atresia Splenic Malformation Syndrome (BASM) include splenic abnormalities like polysplenia and asplenia, cardiac defects, situs inversus, intestinal malrotation, portal vein anomalies and inferior vena cava interruption.

Delay in referral in BA is because of difficulties in differentiating it from physiologic jaundice and identifying an abnormal stool colour. This is a major problem in most parts of the world, especially in developing countries. In India, only 20% of cases that present in most centers are aged less than 60 days [4]. The parents of children with delayed diagnosis usually consult a doctor for persistence of jaundice but a lack of awareness leads to the delay. Both primary health care workers and primary care physicians must be aware of the need to refer infants in whom jaundice persists beyond 14 days of age. It is also vitally important to identify abnormal stool color and investigate infants in whom pale stools persist for 3 consecutive days [5]. Stool cards have been effectively used as a screening tool in countries like Taiwan and Japan [6,7]. The stool card is incorporated in every child health booklet given to the parent at the time of delivery. Abnormal stool colour is reported by the parent or pediatrician to the registry center within 24 hours. In Taiwan, the sensitivity of detecting BA using stool cards improved from 72% to 91% in the span of a single year [6]. Japan also reported a sensitivity of 76.5% and specificity of 99.9% for the stool colour card in the diagnosis of BA [7]. Hence it will be useful for developing countries to use this model and disseminate information

about stool cards to primary care physicians and healthcare workers. The onus of responsibility lies with national pediatric forums to institute a nationwide screening program and play an active role like the yellow alert poster campaign which created awareness among paediatricians throughout the country [5].

Most children with BA have a normal postnatal weight gain and development. The classic triad of jaundice, pale stools and high coloured urine may not be present early in the course of the disease. The liver is firm, and in the initial stages splenomegaly and ascites which are features of portal hypertension may not be obvious. The deceptively "well baby" is another reason for delay in referral. Laboratory parameters show a rise in serum bilirubin with a raised conjugated fraction (>50% of the total) and elevated transaminases. However, these findings are common to most forms of neonatal cholestasis. A raised gamma glutamyl transferase (GGT) is seen in BA, and is often used to differentiate it from neonatal hepatitis. A GGT level of >300 IU/L has a specificity of 98.1% in the diagnosis of BA [8]. There may be an initial coagulopathy responsive to Vitamin K. Persistent coagulopathy and hypoalbuminemia are features of advanced disease and signify synthetic dysfunction of the liver.

Ultrasonography has gained importance as a key diagnostic tool for BA, and has an overall accuracy of 98% [9]. However, this is operator-dependent and can be achieved only in centers where dedicated pediatric sonologists are available. Radionucleotide scintigraphy (Tc99-HIDA scan) has a high sensitivity but poor specificity in differentiating BA from other causes of neonatal cholestasis [10]. It also requires pre-treatment of the infant with phenobarbitone for 3 days prior to the scan and repeated imaging for up to 24 hours to look for isotope activity in the gut. Endoscopic retrograde cholangiopancreatography (ERCP) is technically difficult in young infants and its results are also operator-dependent.

Liver biopsy showing portal tract expansion with edematous fibroplasia and proliferation of anastomosing ductules is suggestive of BA if reported by an experienced histopathologist (***Fig.* 1**). Several Indian studies have reported high accuracies of over 85% for liver biopsies in the diagnosis of BA [11-13]. These studies are from specialist centers with experienced pathologists, and hence the diagnostic accuracy is high [14]. Children with biliary atresia have a nonspecific biopsy diagnosis in as much as 15% of cases [15]. Therefore, in developing countries, relying on a liver biopsy to make a conclusive diagnosis may lead to missed diagnosis of BA in a significant number of children.

The gold standard for the diagnosis of BA is a per-operative cholangiogram which has a diagnostic accuracy of 100%. The procedure involves injecting radio opaque contrast into the gall bladder remnant through a small laparotomy. A diagnosis of BA is made if contrast does not fill the common hepatic duct and intrahepatic ducts. Based on this per-operative cholangiogram, BA is divided into three types according to the Ohi classification with the commonest type being type 3 (***Fig.* 2**) [16]. If the cholangiogram shows a normal extrahepatic biliary tree, a wedge biopsy of the liver is taken and the wound closed. Per-operative cholangiogram has to be undertaken by an experienced surgeon who can differentiate hypoplastic ducts (Alagille syndrome) from atretic ducts thereby avoiding a potentially damaging and unnecessary operation in the former [17].

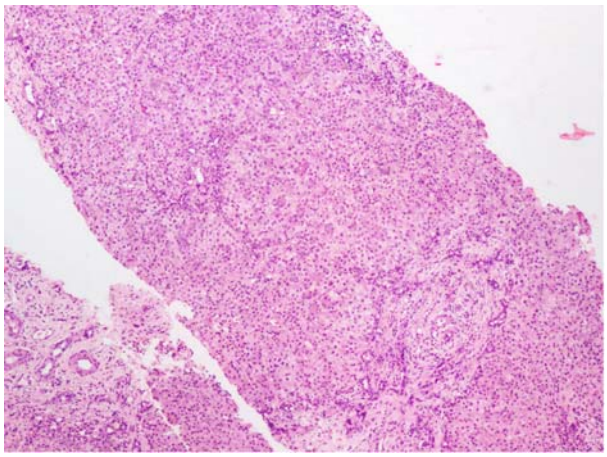

FIG. 1 *Trucut liver biopsy showing portal tract expansion with edematous fibroplasia and proliferation of anastomosing ductules (H&E, ×40).*

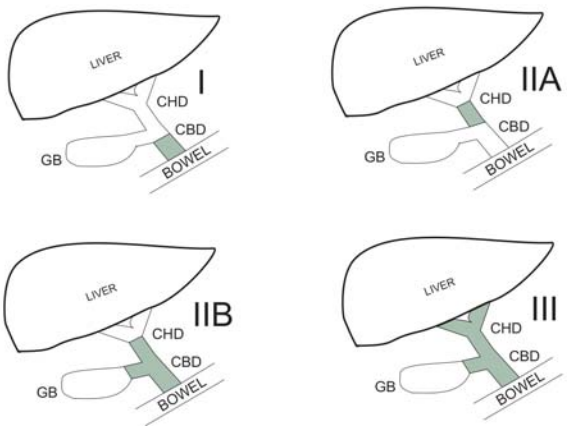

FIG. 2 *Ohi classification of biliary atresia.*
CBD – common bile duct, CHD – common hepatic duct, GB – gall bladder.

To summarize, in an infant with jaundice, pale stools, conjugated hyperbilirubinemia and raised GGT, it is reasonable to perform an ultrasound scan and a liver biopsy to make a diagnosis of BA. In developing countries, where such expertise may not be available in most centers, the child should be referred for a per-operative cholangiogram and liver biopsy at the earliest suspicion of BA. A screening program with stool color card is a must for early diagnosis and should be the priority of healthcare systems. It is equally important to educate primary physicians and healthcare workers about early diagnosis of cholestatic jaundice and to establish a uniform protocol for its management [5].

MANAGEMENT OF BILIARY ATRESIA

The treatment of BA involves a sequential strategy combining Kasai Portoenterostomy (KPE) as first line and Liver transplantation as second line treatment if KPE fails to establish bile flow and/or progressive liver fibrosis and cirrhosis occurs ***(Fig.* 3***)***.

Kasai Portoenterostomy

Described by Professor Morio Kasai in 1959, the goal of this operation is to allow bile from the liver to drain into the small intestine [18]. This operation has undergone several modifications since it was first described and the outcomes have also vastly improved with the use of surgical loupes for magnification and fine sutures for the anastomosis. We prefer a technique which involves division of the left triangular ligament which enables the liver to be partially exteriorized to expose the hilum. The remnant gall bladder is mobilized from its bed and excised along with the biliary remnants. These remnants are meticulously dissected above the bifurcation of the portal vein towards the corners of the hilar ductal plate, where the portal vein and hepatic artery bifurcate into their branches. The dissection of the ductal plate begins from the point where the right hepatic artery divides into its anterior and posterior branches, and continues to the left where the left branch, of the portal vein joins the umbilical vein in the Rex recess. The fibrous remnant in the region of the ductal plate is excised using sharp dissection down to the level of the Glisson's capsule (***Fig.* 4**). Bile is usually found to drain from the right and left corners of this ductal plate. A Roux loop of jejunum is anastomosed around this region to the quadrate and caudate lobes of the liver. Using this technique it is possible to achieve clearance of jaundice in over 50% of children [19,20].

Outcome of KPE

The outcome of KPE is evaluated by the clearance of jaundice (S. bilirubin <2 mg/dL) in 3 months, and the survival of children with their own liver: Native liver survival rate (NLSR). Jaundice clearance leads to alleviation of hepatic fibrosis and the jaundice

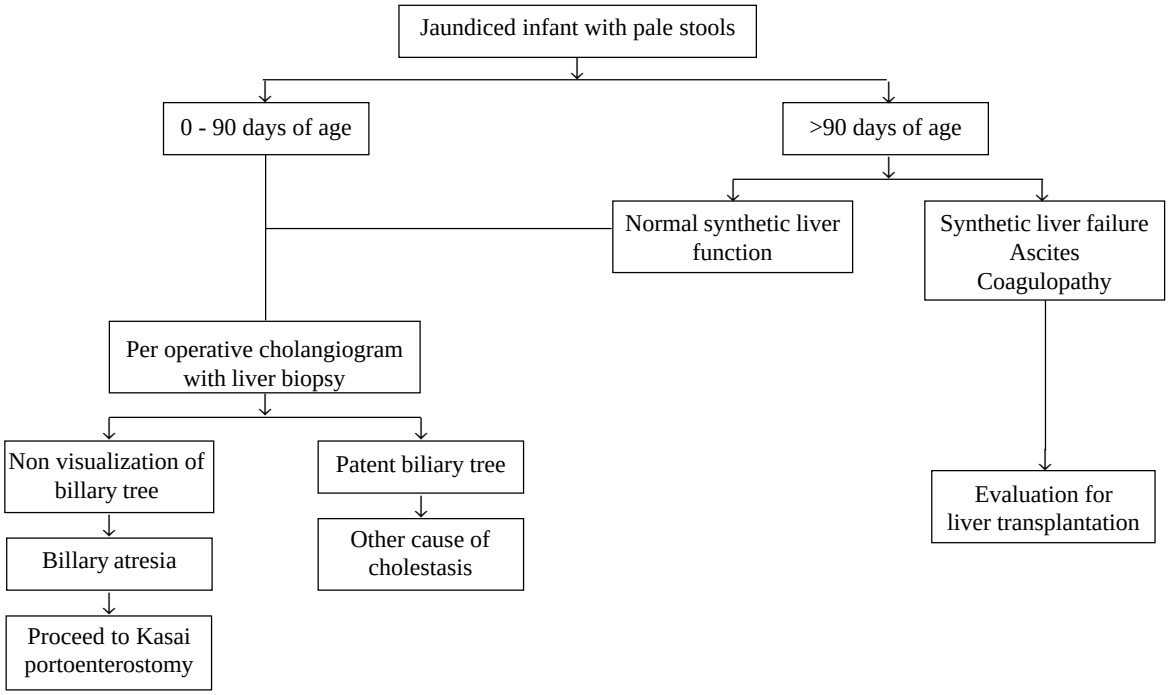

FIG. 3 *Flow chart for the management of children with biliary atresia.*

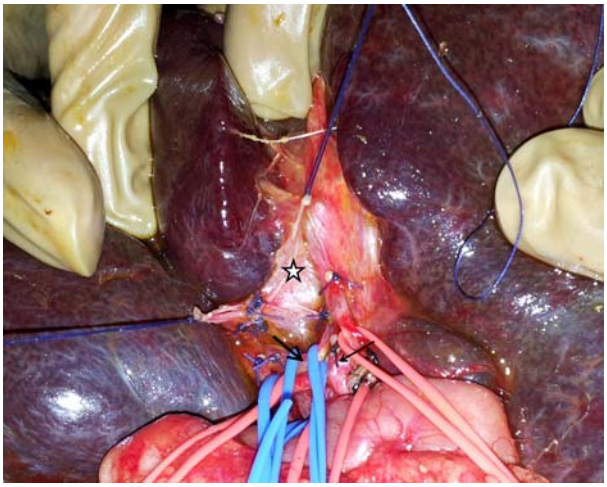

FIG. 4 *Operative picture of Kasai portoenterostomy showing fibrous biliary remnant (star), hepatic artery (thin arrow) and portal vein (thick arrow).*

disappearance rates (JDR) in most series from Japan, France, England and Wales is around 57% [1,19,21]. In 2003, the Japanese Biliary Atresia Registry reported that nearly 53% of children had their own native liver at the end of 10 years [1]. The 10 year NLSR reported from England and Wales in 2011 was 40% [20]. Most studies have shown that 45% of all children will reach their teenage years with their own livers, and 30% will have a truly long-term, symptom-free life with normal liver biochemistry [22-26]. Studies from specialized centers in India have also shown good JDR and NLSR [4,27-30]. In the experience of 26 children from our center over the last 2 years, the JDR was 50% (unpublished data).

Factors affecting the outcome of KPE

Several factors have been shown to adversely affect the outcome of KPE. The outcome is worse in the embryonic or syndromic form compared to the perinatal form because this form represents an early origin of the disease [3]. Ohi type 3 pattern of atresia, the commonest form of BA, is associated with a poor outcome because in this variant the hilar ductules are also atretic in addition to the extrahepatic biliary system [16]. Histological features such as ductal plate malformations [31], cystic dilatation of intrahepatic biliary system [32] and bile lake formation [33] are all associated with poor outcomes. Ductal plate malformations represent the persistence of embryonic ductal structures. Their presence in the liver adversely affects the outcome of KPE because they represent an early severe form of the disease [34].

Portal plate ductules measuring greater than 200 microns were found to correlate with the success of KPE in some studies [27,35]. However, other studies have shown that the size of ductules at portal plate did not have a linear relationship with prognosis [36,37]. Recent studies from India have also shown no correlation between duct diameter and outcome [28,29]. Also, accurate measurement of the size of bile ducts at the portal plate depends on the orientation of the pathology specimen and there can be a subjective variation among pathologists [38]. Aspartate aminotransferase-to-platelet ratio index (APRi) has been used as a surrogate marker for liver fibrosis. A cut-off value of 1.22 has shown to have 75% sensitivity and 84% specificity for macroscopic cirrhosis. Hence, APRi at the time of KPE is a useful adjunct in evaluating severity of liver disease in BA [39]. It also helps to predict native liver survival by reflecting portal myofibroblastic cell activation, fibrogenesis and associated neovascularisation [40].

Age at KPE is an important determinant of jaundice clearance. Data from the Japanese Biliary Atresia Registry reported a good outcome in infants who had KPE earlier than 30 days of age, and a poor outcome after 90 days [1]. Between 30 and 90 days, age at KPE had no impact on outcome. The French National Study reported a definite advantage in performing an early KPE [21]. A recent study from India also showed better outcome of KPE when performed before three months of age [27]. Early diagnosis is important because KPE before 90 days offers a significant advantage in terms of post-operative jaundice disappearance and long term native liver survival [41].

In infants older than 90 days, there is still a significant benefit in performing KPE. Studies have shown JDRs of up to 48% and 10 year NLSRs of up to 40% in these children [1,26,41-43]. Successful KPE has been reported even until the age of 141 days [44]. The performance of KPE after 3 months of age is justified in selected cases because it may obviate the need for liver transplantation. There is a significant advantage to performing KPE even in older children with BA; age alone is not a contraindication. The national consensus report recommended that referring doctors need to be educated that there is no cut-off for late referral [14]. It is up to the specialists (pediatric hepatologists and surgeons) to decide if the child has synthetic liver failure, and hence will not qualify for a KPE.

Another factor that impacts the outcome of KPE is the surgical technique. The success of the operation depends on the meticulous dissection of the liver hilum and the resection of the biliary remnant [45]. Results are better after centralization of management of BA, and upto 24% improvement in outcome can be achieved if the surgery is done in a specialized center [2,19-21]. McKiernan, *et al.* [2] reported that the outcome of KPE was better in centers

having case-loads greater than 5 cases per year. In such specialized centers, the outcome of KPE in children over 90 days was also better [46]. In the national consensus report, it was proposed that the surgical treatment of children with BA should be contemplated only in centers performing at least 6 KPEs a year. Since centers that fulfil this criteria are limited, more and more surgical departments should be encouraged to develop proficiency in handling these cases [14]. In the developing world, where health care systems do not provide for the costs of liver transplant, centralization of management of infants with BA can significantly reduce the need for transplantation [19].

Contraindications to KPE

The only contraindication to KPE is advanced liver disease with an uncorrectable coagulopathy, low albumin, ascites and portal hypertension. The operation is associated with a very high morbidity and mortality in this group because rapid decompensation of liver disease can occur. Approximately 50% of children with BA will be able to clear jaundice, if KPE is performed by experienced surgeons before the onset of advanced liver disease. These children have a reasonable expectation of long-term survival to adulthood with a good quality of life [22].

Postoperative management

The incidence of cholangitis can be as high as 50% for the first two years after KPE [47]. Repeated episodes of cholangitis can lead to early liver failure. Episodes of cholangitis are characterized by fever, recurrent pale stools and septicemia. However, sometimes fever may be the only symptom. Prompt diagnosis followed by intravenous antibiotics for two weeks is required if a pathogen can be identified in the blood or ascitic fluid. Long-term prophylaxis is required with rotating antibiotics in cases of recurrent cholangitis [46]. Post-operative corticosteroids to maximize bile flow has not been found to be of any use in improving the outcome of KPE [48].

These infants also have multiple nutritional deficiencies, and supplementation with Vitamins A, D, E and K is needed. They also have deficits in protein metabolism with low muscle and liver stores of glycogen, which must be supported by feeding regimes to maximize growth potential by providing adequate nutrition [49].

Liver Transplantation

Liver transplantation remains the cornerstone of long-term management of children with BA, and is the commonest indication for transplantation in children. It is needed in more than 50% of children with BA even after undergoing KPE.

Indications

Liver transplantation is indicated in BA in three different clinical settings. It may be necessary in infants who have a delayed diagnosis of BA, and hence have not been subjected to a KPE. These children usually present within one year of age with intense jaundice, liver synthetic dysfunction and failure to thrive. The second group of children are those who undergo a KPE but do not clear synthetic failure. These children usually need transplantation in the first two years of life. The indications in this group include jaundice, portal hypertension and failure to thrive. The third group of children (or adults) are those who have successfully cleared jaundice after the KPE, but have recurrent cholangitis, portal hypertension or hepatopulmonary syndrome. Each of these three groups of patients have their own specific set of issues and challenges during transplantation.

General considerations

The majority of children with BA undergoing liver transplantation are less than two years of age. These children usually weigh less than 10 kg and may even be less than 5 kg, especially those with late diagnosis. Pediatric liver transplantation is a challenging technical exercise. Issues include small recipient size, recipient and graft size mismatch, associated anatomical anomalies and the need for meticulous surgical techniques and peri-operative care. Children with BA can have associated congenital anomalies like BASM. A careful review of pre-operative imaging will help in identifying most of these instances so that the surgeon is prepared and has a plan in place to deal with these issues. Modifications to implantation techniques are usually necessary with the need for additional vascular grafts in these children [50,51]. This has the potential to increase post-operative morbidity [52,53].

Type of liver graft

The source of liver grafts in transplantation can be cadaveric donors or living donors. Whole grafts from pediatric donors are uncommon. In the West, liver grafts for children are usually obtained by splitting healthy livers from cadaveric adult donors. In developing countries, most pediatric liver transplantations performed are split left lateral segment (LLS) grafts from living donors; cadaveric donor living transplantation is much less common. This is because of low deceased donor numbers and the shortage of technical skills to undertake split liver transplantation. Additional concerns regarding

the quality of deceased donor organs and prolonged cold ischemia times also prevent using split liver techniques more consistently. However in experienced units, split liver transplantations are excellent means of improving access of small children for deceased donor grafts. The choice of transplant in these countries ultimately depends on whether the child has a suitable family donor. If so, the transplant can be completed in a timely fashion with good results. The alternative is a prolonged wait for a good quality 'splittable' graft becoming available from a deceased donor.

Mismatch between recipient weight and graft size is a problem in transplantation of children less than 10 kg. This is further accentuated when the recipient weight is less than 5 kg. The usual left lateral graft averages around 250 grams. This gives a Graft Recipient Weight Ratio (GRWR) of over five. In such relatively large grafts, there is a risk of portal hypoperfusion, vascular complications, and graft ischemia/necrosis. Post-operative recovery is also affected due to abdominal compartment syndrome requiring prolonged ventilatory support. Further graft reduction is essential in these cases to reduce the GRWR to less than four. This can be carried out by lateral reduction to decrease the graft volume, the use of segmental grafts, or non-anatomical thinning for both volume and thickness [54,55]. There should be no hesitation in delayed closure of the abdominal wall to prevent abdominal compartment syndrome.

Children with BA who have previously undergone KPE usually have significant intra-abdominal adhesions. The adhesions are usually vascularized and adhesiolysis in this setting is associated with risk of bleeding and enteric injury. Meticulous care should be taken during recipient hepatectomy to avoid injury to the bowel during adhesiolysis. All serosal or full thickness injuries should be repaired immediately so that they are not missed later in the operation. Bowel perforation and peritonitis in children undergoing liver transplantation after KPE is quite common, and a high index of suspicion should be maintained for any unexplained change in clinical course of these children. When in doubt, it is safer to re-explore these children than persist with conservative management until frank signs of peritonitis appear [56].

Portal vein complications

BA is associated with hypoplasia of the portal vein. The etiology of the portal vein hypoplasia is multifactorial and could be related to the early onset hepatic fibrosis in these children which prevents the usual development of the portal vein. Portal vein management in liver transplantation depends on the severity of hypoplasia. In mild cases where portal flow is adequate, a patch can be created using the portal vein bifurcation to anastomose to the donor portal vein (branch-patch technique). Satisfactory flow should be documented with an intra-operative Doppler in these cases. In cases where the portal vein diameter is less than 4 mm, it is safer to use an interposition vein graft between the splenomesenteric vein junction and the graft portal vein. The splenomesenteric vein junction is usually of good size because of the continuous shunting that occurs across this junction.

In children with portal agenesis or a severely atretic portomesenteric system, the options are limited. Meticulous dissection of the root of mesentery can sometimes identify a good quality branch of super mesenteric vein with satisfactory flow. If available, a jump graft may be used for ensuring portal inflow to the graft. When such a vein is not available, portocaval hemitransposition may be a salvage option. Here the infrahepatic cava is used as portal inflow by creating an end–to-end anastamosis between the infrahepatic cava and the graft portal vein. This technique, first reported by Tzakis, *et al*. [57], has since been reported by several others in the pediatric liver transplantation setting either as a primary procedure or as a salvage technique in the re-transplant setting. The procedure is associated with significant early morbidity in terms of pedal edema, renal dysfunction and ascites which usually resolves over time. Lipshutz, *et al*. [58] reported a higher risk of primary non function with this technique, especially when a split graft was used, and suggested that it could be due to high portal flow causing a relative small for size syndrome in these children.

Post-transplant portal vein complications in the form of portal vein thrombosis or portal stenosis have been reported in approximately 15% of children. Risk factors include small age, low weight, small caliber portal vein and emergency transplant [59]. Early portal vein thrombosis presents with worsening coagulopathy and hyperammonemia, and requires immediate surgical exploration. Serial ultrasound Doppler scans (twice daily for the first three post-operative days followed by once daily in the first week) will help in early diagnosis. Late portal vein stenosis is usually diagnosed on routine Doppler ultrasound. While mild stenosis can be conservatively managed, significant stenotic lesions are best treated by stenting and anticoagulation.

Outcome

Liver transplantation for BA has a very good outcome. Most large series from the West have shown patient and graft survival rates at 10 years of 81-86% and 71-73%, respectively. Previous KPE has not been associated with

patient mortality in any of these studies [60-63]. Recent Indian studies have shown patient survival rates ranging from 70-90% [64,65]. At our center, 144 pediatric liver transplants have been performed over the last 5 years. Of these, 65 (45.1%) were performed for biliary atresia with 90% patient survival rate. Studies have also shown growth failure to be predictive for patient death and hence suggest a significant role for nutritional support and early consideration of liver transplantation before nutritional and growth failure occurs [60,66].

Role of primary liver transplantation

Liver transplantation as the primary modality of treatment for BA is a contentious issue [67]. Liver transplantation is a major surgery, is expensive, and submits the child to lifelong immunosuppression. According to a recent study on the health status of children alive 10 years after liver transplant, only 32% achieved an "ideal profile" as defined by first allograft, stable on monotherapy, normal growth and absence of common immunosuppression-induced sequelae. Impaired growth was seen in 23%, renal dysfunction in 9%, and post-transplant lymphoproliferative disease (PTLD) in 5%. These patients also had a lower health-related quality of life score than matched healthy children [68].

A successful KPE can avoid transplantation in upto one-third of children. In a large proportion of children, it delays the need for liver transplantation thereby delaying the need for immunosuppression. Clearance of jaundice after KPE provides an opportunity to improve the nutritional status of the child. It will also give the family an opportunity to come to terms with the need for transplant and the associated financial implications. Even if a transplant is required at an older age, it is safer because the risk of technical complications is lesser, and the risk of mortality is lower than in infancy [60,63]. The only indication for primary liver transplantation for BA is in children who have synthetic liver dysfunction and features of portal hypertension. In these children, a KPE will lead to liver decompensation.

The cost of liver transplantation for most families in developing countries is prohibitive. The cost factor also favours KPE over primary liver transplantation in children with BA.

CONCLUSIONS

Inclusion of stool color cards as part of a screening program in the neonatal period will greatly improve early detection of BA. Outcomes will improve if it is diagnosed at the earliest after birth, and the child is referred to an experienced pediatric hepatobiliary unit for evaluation and early KPE. If an early KPE is performed, nearly half of all children will reach teenage years with their own livers, and about a third will have a truly long-term, symptom-free life with normal liver biochemistry. Following KPE, liver transplantation is indicated in children in whom the KPE fails or in those who develop portal hypertension and recurrent cholangitis despite a successful KPE. Children with BA need a primary liver transplantation only if the diagnosis has been missed in early infancy, resulting in liver failure. Sequential treatment combining KPE as first-line and liver transplantation as second-line results in 90% survival for children with BA.

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