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Biliary Atresia: Hepatic Portoenterostomy or Liver Transplantation? Experience of a Single Center and Review of the Literature

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Abstract

Introduction: Biliary atresia is a rare disease of infancy. Over the last 30 years it has evolved from a fatal disease, to one where long-term survival can be achieved with the use of palliative surgery or liver transplantation. Our goal is to present the experience of a University Pediatric Surgical Clinic, and discuss the implications of the two main surgical treatments, including latest advances in the area.

Patients and Methods: Through a review of the records of our University pediatric surgical clinic, four patients were identified that were diagnosed with biliary atresia. Their records were reviewed, including the type of biliary atresia, the treatment and the outcome.

Results: Three patients underwent a hepatic portoenterostomy procedure, all within 60 days from birth, whereas the fourth patient is awaiting a liver transplantation. From the three patients undergoing the Kasai operation, one is doing well, without any need for further treatment 4 years after the surgery. In the other two patients, in one of them the portoenterostomy procedure failed and the patient underwent a successful liver transplantation, whereas the other one is on the waiting list for a liver transplant.

Conclusion: There is a debate as to the timing and type of optimal surgical therapy for biliary atresia. As these cases show, these two treatments are not mutually exclusive, but rather have the ability to complement each other. This underscores the need for these patients to be evaluated at centers with experience in all aspects and modes of treatment for biliary atresia.

Keywords: Biliary atresia; Pediatric liver transplantation; Kasai procedure; portoenterostomy procedure

Introduction

Biliary Atresia (BA) is a rare condition that occurs in about 1:15,000 live births (1.5 times more common in females) and represents the most common surgical cause of neonatal jaundice and the main indication for Liver Transplantation (LT) in children [1-3]. BA is a progressive, fibro-obliterative cholangiopathy that affects both the extra- and intrahepatic biliary tree to various degrees, resulting in obstructive bile flow, cholestasis and jaundice in neonates [4-6]. If this condition is left untreated, progressive liver cirrhosis leads to death by the age of two years. Biliary atresia is classified based on the level of extrahepatic obstruction of the biliary tree [5]. In type I BA (about 5%) the biliary tract is obstructed at the level of the common bile duct. In type II (about 2%), obstruction occurs at the level of the common hepatic duct. In type III (> 90%) BA, the most proximal part of the extrahepatic biliary tract in the porta hepatis is obstructed and fibrotic, without any macroscopic remnants of the hepatic ducts [4].

Even in the case of type III BA, microscopic residual bile ductules of variable size at the level of the porta hepatis remain in continuity with the intrahepatic biliary tree. Kasai portoenterostomy, initially described in 1959, is a palliative operation performed to restore bile drainage from these microscopic residual ductules [7]. Liver transplantation is indicated in the case of failure to establish biliary flow, and biliary atresia remains the most common indication for liver transplantation in children, accounting for about 75% of transplantations in those younger than two years old (European Liver Transplant Registry 2005) [8].

In this paper we present the experience of a University Pediatric Surgical Clinic with the Kasai procedure. The presentation of the four cases is followed by a review of the two main surgical treatments of BA, the hepatic portoenterostomy and liver transplantation, including the advantages and disadvantages of each. The goal is to show that these two approaches are not necessarily mutually exclusive, but rather that they may complement each other.

Case 1

A two month old male patient was transferred to our unit with obstructive jaundice. The child was being observed in the neonatal intensive care unit of our hospital due to a cardiological problem, which had been diagnosed prenatally and for which supportive therapy was required. He had been delivered normally on the 38th week of gestation and his weight at birth was 2660 gr. During his

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hospitalization in the intensive care unit, pediatricians noticed the prolonged jaundice. Laboratory tests confirmed the clinical presentation with the values of total and direct bilirubin being 6, 11 gr/ dl and 5, 76 gr/ dl respectively. The rest of the liver function tests were also affected, with aspartate aminotransferase (SGOT) and alanine aminotranferase (SGPT) values of 239 IU and 178 IU respectively. Blood tests were followed by imaging studies - ultrasound, magnetic resonance cholangiopancreatography and technetium 99m scintigraphy- that suggested the presence of an extrahepatic biliary atresia type II.

With the working diagnosis of biliary atresia, the patient was led to surgery and a Kasai portoenterostomy was performed, at the age of 60 days old. Although he recovered well from the operation, jaundice seemed to persist. A new scintigraphy performed 20 days after the reconstruction, showed no bile excretion into the small bowel and the patient was kept under close follow up. Three months later he was re-admitted because of further elevation in the bilirubin values, with direct bilirubin being as high as 12,6 gr/ dl. Two scintiscans, on admission and three months later, revealed once more the persistent intrahepatic cholestasis and the absence of bile flow into the gastrointestinal lumen. Due to his deteriorating clinical status and the radiological absence of bile from the gastrointestinal lumen, and thus the presumed failure of the Kasai operation, the patient is being considered for living donor liver transplantation.

Case 2

This was a male patient who was transferred to our unit due to persistent elevation of the direct bilirubin by the fortieth day of life. The child had been delivered by caesarian section on the 40th week and was in good general condition, presenting with normal growth and weight for his age. Moreover, there was no evidence of coexisting anomalies. The value of direct bilirubin was about 7 mg/ dl on admission, with additional elevations of γ-GT, alkaline phosphatase, SGOT and SGPT. The abdominal ultrasound revealed absence of a normal gallbladder, the magnetic resonance cholangiopancreatography showed absence of a patent extrahepatic biliary tree and a technetium 99 scintigraphy confirmed the diagnosis of extrahepatic BA. A Kasai portoenterostomy was performed at 45 days old. The postoperative course was uneventful and the child was discharged in good condition, with significant reduction of the bilirubin values and the rest of the liver function enzymes, evidence of a successful procedure.

Since the portoenterostomy he was readmitted just once, because of an episode of acute cholangitis, and has not had any other complications since. Six years after the operation, liver function remains within normal range and the child has a normal development.

Case 3

The third case is about a two month old boy, who was referred with a diagnosis of extrahepatic BA type III, after presenting locally with persistent jaundice. No other congenital anomalies were identified. His weight on admission was about four kilograms and laboratory tests showed a direct bilirubin of 7, 9 mg/ dl, γ-GT=633 U/l, and SGOT and SGPT of 300 U/l and 500 U/l respectively. Radiological examination, including ultrasound, abdominal computed tomography, and magnetic resonance cholangiopancreatography and scanning with technetium 99, established the diagnosis of extrahepatic BA and due to the deterioration of his clinical and biochemical status, the young patient underwent a Kasai portoenterostomy. The postoperative course was uneventful, with a slow drop in the bilirubin during the immediate postoperative period.

However, two months after the procedure the patient was readmitted to the hospital, because of pain, fever and jaundice, suggesting an acute cholangitis attack. After initial conservative management with antibiotics, a technetium 99 scintigraphy was performed, revealing a nonfunctional anastomosis with no significant excretion of the radioisotope in the gastrointestinal tract. During the next few months, the baby presented with several episodes of acute cholangitis and in repetitive scintigraphies there were signs of remarkable intrahepatic cholestasis. By the age of fifteen months the jaundice was severe and persistent and the patient's general condition was getting worse, with the episodes not responding to the antibiotics. Liver transplantation seemed to be the only reasonable decision. After a detailed discussion with the parents, the child was referred for living donor related liver transplantation, which does not currently take place in our country. Today, almost a year after the transplantation, the patient is in good condition with satisfactory liver function and without complications related to the procedure.

Case 4

A two- month old male baby was referred to our department because of persistent obstructive jaundice. The child had been delivered normally and had a history of an upper respiratory infection at the age of forty days old. He was also taking antibiotics for a urinary tract infection around the time of his admission. The parents mentioned the presence of pale stool for the last month. At the time of admission to our hospital, the child presented with jaundice and hepatomegaly, though he was in good general condition otherwise. Other causes of neonatal obstructive jaundice had already been ruled out. Laboratory findings were indicative of a hepatic disorder with biliary stasis, as SGOT level was 180 U/ l, SGPT 128 U/ l, γ-GT 852 U/ l, alkaline phosphatase 951, direct bilirubin 6,33 gr/ dl and indirect bilirubin 7,06 gr/ dl. Renal function appeared to be normal, while white blood cell, red blood cell and platelet counts were within normal range too.

An abdominal ultrasound was done which revealed normal liver structure, a string-like image of the gallbladder and inability to recognize the bile duct. These findings were confirmed by a magnetic resonance cholangiopancreatography and a technetium 99m scintigraphy, which showed no excretion of the radioisotope into the small bowel. Therefore all of the previous imaging studies were indicative of the presence of BA of the third type. A liver biopsy under computed tomography guidance was performed with the result revealing intrahepatic cholestasis with portal space fibrosis and nodular liver structure, indicative of BA with liver cirrhosis.

The young patient remained in good condition with stable bilirubin levels and, since there wasn't a need for an immediate operation, he was placed on the list for orthotopic liver transplantation with a cadaveric graft. Given his age he was considered not to be a good candidate for a Kasai procedure, and so he was evaluated for both living and cadaveric liver transplantation, whichever would become available first. The child has been under close follow-up, waiting for a liver transplantation.

Discussion

Biliary atresia (BA) is a progressive fibro-obliterative disease of the intra- and extra-hepatic biliary tree, leading to biliary obstruction, cholestasis and icterus in neonates. It is essentially a disease of the neonatal period and does not present later in life. Although it has been extensively studied, the cause of BA has not been identified, and many different hypotheses have been proposed. These include, among others, a defect in early bile duct development, a perinatal infection with various hepatotrophic viruses, and an abnormal hepatic arterial supply [9-11]. Even though the etiology may not be clear, the course of the disease is standard as it invariably leads, if untreated, to cirrhosis, liver failure and death.

Regarding its treatment, the mainstay and the first line in most pediatric surgical centers, is the biliary-enteric anastomosis without mucosal approximation, known as the Kasai procedure [12]. This provides restoration of bile flow in approximately 60% of patients. Unfortunately, despite multiple attempts at technical improvements of the hepatic portoenterostomy, recurrent cholestasis with episodes of cholangitis and portal hypertension result in the development of end-stage liver disease [13]. Eventually the majority of children with BA will require Liver Transplantation (LT), which becomes the only option for long-term survival. However, the advantage of postponing the LT into later childhood or adolescence remains, as the technical demands of the LT decrease with the growth of the child, whereas the chances of finding an appropriate graft increase. Additionally, the period of exposure to immunosuppression is shortened and does not occur during as critical a period of development. Even so, it is not always possible to postpone the LT, and thus pediatric LT has continued to evolve with the introduction of reduced-size liver transplantation, split-liver transplantation or living donor liver transplantation.

In this paper we present four young patients with a similar presentation and a diagnosis of biliary atresia. Their treatment plans had different outcomes, depending on the patient's age and the response to the Kasai portoenterostomy (Table 1). Three of the four infants underwent a Kasai portoenterostomy, which was completely successful in one of the children. In the other two, the problems with biliary excretion remained, thus making it necessary to proceed to liver transplantation. Even in these cases however, there was the benefit of delaying the liver transplantation, which means less exposure to the immunosuppressive medication, as well as fewer technical challenges. Similarly, in the last case where the Kasai procedure was not deemed as the best solution, given the combination of biliary atresia and cirrhosis, the decision was made to attempt to wait before proceeding with a liver transplantation for the reasons mentioned above. Should it be possible to wait till the age of 10-12 months, then a cadaveric hepatic graft becomes more of a possibility. What has been critical in achieving a satisfying long-term outcome is the ability to provide a continuum of care to these patients. Specifically, they need to be evaluated for both the Kasai portoenterostomy and a potential liver transplantation at the time of presentation, as these two types of surgical treatment often end up complementing each other. An advantage at our university has been the close cooperation between the Pediatrics, Pediatric surgery and Transplantation surgery departments, which allows the evaluation of these patients by all the different teams.

The Kasai procedure aims at excising all extrahepatic biliary remnants to allow a wide portoenterostomy reconstruction onto a portal plate. Overall, the success of the Kasai procedure is marked by the clearance of the bilirubin and its return to normal within 6 months. There are many factors that can influence the outcome of the surgery, including some that cannot be controlled (degree of cirrhosis, absence or paucity of biliary ductules at the plate), whereas others can be altered (surgical experience, cholangitis). The relation between age of the infant and the success of the Kasai procedure is not linear, although there is agreement that up to 80-100 days is the ideal period, as after that fibrosis is detrimental [14]. In centers with experience, approximately 50-60% of infants will clear their jaundice and bile flow will be restored [15-16]. In these cases a good quality of life with the native liver can be achieved, whereas in those infants with no effect from the Kasai procedure (apparent in 2-3 months), early LT may be the only solution. The importance of surgical experience has led many countries, including France and the UK, to centralize services for BA, thus being able to achieve clearance of jaundice just below 60% after the Kasai procedure, and an overall 4-year survival of 89% [17-18]. Most frequent complications include cholangitis and portal hypertension. Cholangitis most commonly occurs in the first year following primary surgery in about 30-50% of children, whereas portal hypertension depends on the degree of established fibrosis prior to the surgery and the response to the surgery. Specifically, in those infants who fail and need early LT, about 30% will have a variceal bleed [19].

Regarding LT, interestingly enough the first attempt at a clinical LT was in 1963 in a child with BA [20]. Despite the fact that the origin of LT was in the pediatric population, the majority of accumulated experience since then has been in adults, mainly due to the donor organ shortage and the technical challenges posed by the procedure in children. Additionally, the transplant experience for BA was originally affected by reports that BA patients had a worse outcome than children undergoing liver transplantation for other causes of hepatic failure. The reason for this was that these inferior outcomes were the result of trying to salvage a failed Kasai procedure in a child who is now malnourished with portal hypertension and liver failure and a smaller for size recipient. Currently, with the improvements in technique, as well as in immunosuppressive medications, BA is the most common indication for LT in children. Unsuccessful Kasai portoenterostomy and refractory growth failure are the main indications among children with BA, although there are a large number of other indications, including advanced liver disease, refractory ascites, variceal bleeding, recurrent cholangitis, progressive cholestasis, intractable pruritus and hepatopulmonary syndrome,

Table 1: Management of patients with biliary atresia. (LDLT: Living Donor Liver Transplantation).

	Type of Biliary Atresia	Age at the time of the Kasai operation (days)	Follow-up before failure of Kasai (mos)	Outcome
Case 1	II	60	6	Waiting for LDLT
Case 2	III	45	48	Functioning Kasai
Case 3	III	60	15	Well, a year after LDLT
Case 4	III	No Kasai operation	-	Waiting for cadaveric or LDLT

among others [21]. Most patients with BA require LT during infancy and thus small recipient size necessitates the use of technical variant grafts, such as the living donor or the split-liver grafts. This fact together with the previous portoenterostomy surgery means that the transplant team has to face issues, such as the technical challenges of hepatic arterial anastomosis and biliary reconstruction, as well as the limited intra-abdominal space with the small recipient and the adhesions from the previous surgery causing problems with closure and increasing the risk of bowel perforation [6]. Despite the improvements in microsurgical techniques, certain issues remain such as the higher risk of portal vein thrombosis in these patients after LT [22]. It is believed that this is due to reduced portal flow in children with portal hypertension leading to decreased portal vein diameter, in addition to the inflammation that is thought to be present with BA, affecting the hepatoduodenal ligament and the area of the portal vein [23]. This is even more prevalent after living donor liver transplantation, because of the increased challenge of this variant graft. An argument in favor of LT for children with BA are the occasional (reported incidence of 1%) reports of hepatocellular carcinoma in these patients, which make LT the definitive treatment [24].

The challenge in the treatment of BA is finding the appropriate and timely treatment and in many cases the appropriate sequence of treatments. In general, over half of the patients normalize their bilirubin after the Kasai portoenterostomy within six months and achieve actuarial native liver 5-year survival of 40-60% [25]. In this report by Sokol et al., which expressed the findings of a National Institutes of Health Workshop in 2006, it was strongly reaffirmed that early diagnosis (< 30-45 days of life) of the biliary atresia, combined with earlier management with a Kasai portoenterostomy before 60-90 days of life was critical to achieving good results, with overall 2-5year survival ranging from 85-91% in most series [25]. As a result currently about 20% of patients with a Kasai portoenterostomy survive into adulthood with their native liver, with serum bilirubin after the procedure being the strongest predictor [25]. On the other hand, a successful liver transplant procedure at some later point in life should be a realistic aim for the majority of infants with BA. A review of the long-term experience of one of the major centers for liver transplantation for BA, with 190 consecutive patients undergoing LT for congenital BA between 1984 and 1996, revealed 1, 2, and 5 year actuarial patient survival rate of 83%, 80% and 78% respectively, whereas the graft survival rates were 81%, 77% and 76% respectively [26]. A multivariate analysis of this data revealed that pretransplant total bilirubin, UNOS status, and graft type (whole or split) predicted patient survival. Among patients undergoing LT for BA, 5-year patient and graft survival ranged from 85-98% and 70-98% respectively [21]. Based on these excellent results of LT for BA, some go as far as to suggest primary LT without a previous Kasai procedure. The reason is the combination of the good results of LT and the increased risk of major perioperative complications in children undergoing LT after a prior portoenterostomy [27]. Newer techniques may change the perception of the Kasai procedure, as the role of minimally invasive techniques is being explored. The first laparoscopic Kasai procedure was reported in 2002 by surgeons from Brazil [28]. What is not clear is whether this laparoscopic procedure provides benefits other than the cosmetic part and the shorter length of hospitalization, as survival appears to be lower with the native liver after laparoscopic compared to the open procedure [29].

The above mentioned issues show that although the care of children with BA has improved tremendously in the last decades, there are several controversies and dilemmas remaining as to the best care of these fragile patients. We have to understand that we know more about the treatment, than about the pathogenesis of the disease, and certainly one would hope that achieving an increased understanding of the mechanism of the disease would help one devise a better long-term treatment. More importantly, a lesson that needs to be stressed is the importance of establishing national or regional centers and cooperation in dealing with these patients, as the one thing that has been shown to lead to a successful outcome, is experience.

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