

Long-Term Outcome of Children with Biliary Atresia after Kasai Surgery in Iranian Infants

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Abstract

Aim: The aims of the present study were to evaluate the long-term prognosis of children with biliary atresia after the Kasai surgery and to analyze the present status of survivors retaining their own liver function.

Background: Biliary atresia is the most common cause of pathologic infantile jaundice that results from obstructions of extra hepatic bile ducts due to inflammation and fibrosis. It is a progressive disorder and gradually results in cirrhosis, portal hypertension and hepatic failure. The disease progression to cirrhosis and hepatic failure could be prevented with Kasai surgery.

Method and patients: This is a descriptive retrospective cohort study in which we evaluated patients with biliary atresia who admitted between 1998 and 2008 and underwent Kasai surgical procedure.

Results: A total of 49 patients had Kasai surgery. Patients' survival rates were 14.3%, 8.1% and 2.1%, 2-5, 5-10 and >10 years after the surgery, respectively. The incidence of cholangitis was 59.1% and gastrointestinal bleeding 38.7% following the surgery. Four patients had liver transplantation (8.1%) and only 2 survived (50%). The survival rates varied significantly depending on the age at Kasai operation. Of the 10 patients who underwent Kasai procedure during the first 8 weeks of life, 6 survived (60%) and 4 died. Of the 23 patients who had Kasai surgery between 8-12 weeks of life, 4 survived (17.3%) and 19 (82.6%) died. Of the 16 patients who had kasai operation after 12 weeks of life, 2 survived (12.5%) and 14 (87.5%) died.

Conclusion: This clinical trial confirms previous studies that Kasai surgery is an effective procedure for the treatment of children with biliary atresia and that the long-term survival rate can be improved if Kasai operation is performed before the first 8 weeks of life.

Keywords: Kasai; Biliary atresia; Liver transplantation; Outcome

Introduction

The most common surgically correctable liver disorder in infancy is biliary atresia. The incidence of biliary atresia (BA) is estimated between 1 in 800 and 1 in 16000 live-born infants [1]. It is an inflammatory disorder of the biliary tract which affects the extra hepatic and intrahepatic biliary trees, and eventually results in complete biliary tract obstruction and development of liver cirrhosis [2].

BA is the most important surgically correctable cause of cholestatic jaundice in the neonates and is the most common cause of liver transplantation in children. If untreated it can result in cirrhosis of liver and even death within the first few years of life. Surgical treatment is usually performed in attempt to restore normal bile flow. The Kasai portoenterostomy should be done as soon as possible. The prognosis seems to be better in infants operated on before 90 days of age [3]. Factors affecting prognosis include: type of BA, age of patient at time of surgery, postoperative bile flow occurrence, episodes of postoperative cholangitis, postoperative long-term antibiotic therapy

and steroid administration, cyst formation in intrahepatic tree and occurrence of liver cirrhosis [4].

According to anatomical bases, biliary atresia is classified which indicates the level and severity of the obstruction. Japanese and Anglo-Saxon classification describes 3 main types which are used more commonly. In distal type (type I), atresia is limited to the common bile duct and the gallbladder and hepatic ducts are patent. In type II, atresia affects the hepatic duct, but the proximal intrahepatic tree is intact (i.e., proximal type. There is a sub classification: type IIa, where a patent gallbladder and patent common bile duct are present (sometimes with a cyst in the hilum, i.e., cystic BA. And in type IIb, the gallbladder as well as the cystic duct and common bile duct are also abstracted due to fibrosing inflammation. Type III, describes cases with discontinuity of right and left intrahepatic hepatic ducts, and of the entire extra hepatic biliary tree which called complete biliary atresia. In French classification the designation of the types IIa and IIb as types 2 and 3 results in a total of four types [5]. In most cases, BA is complete (Japanese/Anglo-Saxon type III, 73%) or near complete (type IIb, 18%), with "cystic" BA and "distal" BA being infrequent (types IIa and I, 6% and 3%, respectively [3].

Clinical manifestation of biliary atresia and cholestasis occur early in infancy (1-2 months) but otherwise the child is healthy. The most

common clinical features include jaundice with conjugated hyperbilirubinemia beyond 2 week of life [6]. It is very important to examine stool color to make the diagnosis of biliary atresia at correct time [7]. There is white stool and dark urine as well as hepatomegaly. But hepatomegaly may not be evident in all cases. Usually a complete work-up of cholestatic diseases is performed to confirm the diagnosis and exclude other liver diseases with early presentation. In ultrasonographic examination the gall bladder may not be visible in many patients. In dynamic scintigraphy (HIDA scan) there is no bile passage to the intestine or liver [8].

Material and Method

Between 1998 and 2008, 146 patients admitted for BA and underwent Kasai's surgery at the Children medical Center in Tehran, Iran. Inclusion criteria were confirmation of extra hepatic biliary

atresia and performance of surgical intervention. Patients with diagnoses of jaundice other than extra hepatic biliary atresia, patient's not undergone surgical operation and those with incomplete follow up following surgery were excluded.

All ethical issues were considered and when it was necessary we called the patients or their parents. Data on patient age, sex, season of year, type of atresia, method of surgical intervention, life longevity following surgery, gastrointestinal bleeding, cholangitis, or liver transplantation was also obtained.

Results

Of 146 patients studied 113 fulfilled the inclusion criteria. All had documented extrahepatic BA. Following tables we summarized some of the findings (Tables 1-4):

| Sex | Frequency | Percent |
|--------|-----------|---------|
| Male | 48 | 42.4% |
| Female | 65 | 57.6% |
| Total | 113 | 100% |

Table 1: Sex distribution of patients.

| Type of disease | Frequency | Percentage |
|-------------------------------|-----------|------------|
| Extra hepatic Biliary atresia | 113 | 77.4% |
| Intrahepatic Biliary Atresia | 11 | 7.6% |
| Neonatal jaundice | 16 | 10.9% |
| Cystic fibrosis | 1 | 0.7% |
| Fat storage disease | 1 | 0.7% |
| Galactosemia | 2 | 1.4% |
| Inspissated bile syndrome | 1 | 0.7% |
| Hypoplasia of bile ducts | 1 | 0.7% |
| Total | 146 | 100% |

Table 2: Frequency of diseases in patients presenting with cholestasis (suspected as biliary atresia).

| Season | Frequency | Percentage |
|--------|-----------|------------|
| Spring | 24 | 21.2% |
| Summer | 19 | 16.9% |
| Autumn | 32 | 28.3% |
| Winter | 38 | 33.6% |
| Total | 113 | 100% |

Table 3: Seasonal distribution of extra hepatic biliary atresia.

| | Frequency | Percentage |
|---------|-----------|------------|
| Term | 89 | 78.2% |
| Preterm | 24 | 21.8% |
| Total | 113 | 100% |

Table 4: Distribution of patients according birth age (term or preterm).

According to patients birth weight, 4 cases were under 2 kg (3.5%), 64 cases had birth weight between two to three kg (3.6%) and 41 had 3-4 kg (36.3%) and 4 cases had more than 4 kg birth weight (3.5%). According to time of appearance of jaundice 26 had appeared before 2 weeks (23.1%), 55 cases had appeared in third or fourth week (48.65%), 23 cases between 5th and 6th week (20.35%) and 9 had appeared after 6th week (7.9%). There was situs inversus in 3 cases and one case had malrotation, 2 had inguinal hernia and 4 congenital heart anomalies (one cyanotic and 3 non cyanotic) as coexisting anomalies.

From 113 cases of extra hepatic biliary atresia Kasai surgery was performed on 78 cases (69%). In 35 cases Kasai surgery was not performed because of frank liver cirrhotic changes at laparotomy in 19 cases, 2 cases with severe cardiopulmonary disease, and in 14 cases parents prevented surgery. Of 78 operated patients there was only proper follow up in 49 cases. From these 37 died (75.5%), 7 cases (14.3%) lived up to 5 years, 4 cases (8.1%) for 5 to 10 year, and one case (2.1%) lived between 10 to 15 years.

In 49 cases with good follow up 4 patients (8.1%) had liver transplantation of whom 2 (50%) died. There was cholangitis in 29 (59.1%), GI bleeding in 19 cases (38.7%) and ascites in 24 cases (48.9%) and esophageal varicose in 14 cases (28.5%).

According of surgical intervention time from 10 patients operated before 8 weeks 6 cases were alive (60%) and 4 cases died (40%). From 23 cases operated between 8th to 12th week of age 4 cases remained alive (17.4%), 19 cases died (82.6%). In 16 cases operated 12th week age 2 cases were remained alive (12.5%) and 14 cases died (87.5%).

In this study 16 cases (14.2%) had TCS sign in sonography and the other 97 cases (85.5%) were negative in this regard. In the other word this test has 14.2% sensitivity and false negative results are 85.8%.

In HIDA scanning 113 case were positive (100% sensitivity), and false positive results in other disease were 13 cases (27.2%). So there is 72.8% specificity in this test.

Discussion

Destruction of intra- and extra hepatic parts of the biliary system leads to cirrhosis and ultimately liver failure and is the commonest indication for liver transplantation in children with BA. BA can be associated with laterality malformation also known as BA Splenic Malformation (BASM) or "embryonal" BA. This condition occurs in 10 to 15 percent of infants with BA [9]. Laterality malformations include situs inversus, asplenia or polysplenia, malrotation, interrupted inferior vena cava, and cardiac anomalies. Children with BASM have poorer prognosis in comparison with those with perinatal biliary atresia [10]. In some parts of the world about 10% of cases of BA have other congenital abnormalities [11].

In the present study, we observed 3 patients with situs inversus, malrotation in 1, inguinal hernia in 2 and congenital heart anomalies in 4 (one cyanotic and 3 non-cyanotic) as coexisting anomalies. In a study reported by Masaki et al., congenital associated anomalies were found in 19.6% of the children including 33 with polysplenia [12]. Some studies showed that there may be seasonal variation and clustering of cases [13], but these observations were not confirmed in other studies [14]. In our study Seasonal distribution was 33.6% winter (38 cases), 28.3% autumn (32 cases), 21.2% spring (24 cases), and 16.9% summer (19 cases).

In our study 89 cases (78.8%) was born term and 24 (21.2%) preterm. Although BA is not common in preterm child some of premature infants had neonatal jaundice.

Kasai surgery was performed on 78 cases (69%). In 35 remaining cases Kasai surgery was not performed because of frank liver cirrhotic changes at laparotomy (n=19), severe cardiopulmonary disease (n=2), and parental refusal from the surgery (n=14).

BA that is confirmed by cholangiography, a Kasai procedure (hepatopertoenterostomy [HPE]) should be performed promptly. The aim of this operation is the attempt to restore bile flow from the liver to the proximal small bowel [15]. For this procedure, a roux-en-Y loop of bowel is created by the surgeon and directly anastomosed to the hilum of the liver, following excision of the biliary remnants and portal fibrous plate.

If successful, the remaining small patent bile ducts will drain into the roux limb and jaundice will start to resolve in the weeks following surgery. If unsuccessful, bile drainage is not achieved, and the child remains jaundiced. If there is persistent jaundice three months after the Kasai, the patient should be referred for liver transplant evaluation.

There are many factors, which will influence surgical outcome. Some are unalterable (e.g. degree of cirrhosis or fibrosis at presentation; absence of, or paucity of, microscopic bile ductules at the level of section) and some are subject to change (e.g. surgical experience, untreated cholangitis). In larger studies from the UK and France, prognosis in children with BASM was poorer in comparison with non-symptomatic infants. Some reasons of increased mortality in this group are the presence of associated malformations specially, severe congenital cardiac disease or hepatopulmonary syndrome [11]. The long-term survival rate is specially correlated with the age of the patient underwent the Kasai's operation [16].

In our study, 10 patients operated before 8 weeks, of these 6 cases were alive (60%) and 4 cases died (40%). From 23 cases operated between 8th to 12th week of age 4 cases remained alive (17.4%), 19 cases died (82.6%). In 16 cases operated 12th week age 2 case were remained alive (12.5%) and 14 cases died (87.5%).

In a study at Taiwan [16] patients less than 60 days old at the time of surgery had a five-year survival rate of 44.8% and a ten-year survival

rate of 39.7%. Those between 61 to 90 days old at the time of surgery had a five-year survival rate of 30.8% and a ten-year survival rate of 30.8%. Patients between 90 to 120 days old at the time of surgery had a five-year survival rate of 32.0% and a ten-year survival rate of 24.0%. Patients more than 120 days old at the time of surgery had a five-year survival rate of 15.8% and a ten-year survival rate of 10.5%.

In fact BA is the most common indication of liver transplantation in infants and children and most cases of biliary atresia needs this operation in their life. At least 60 to 80 percent of patients with BA will require liver transplantation, even with good management. Indications of liver transplantation for patients with BA include: Primary failure (complete lack of bile drainage) of the Kasai hepatoportoenterostomy, refractory growth failure. This is common in children with cholestasis, complications of portal hypertension (if these cannot be managed with other measures), repeated bleeding from varicotic veins, refractory ascites that leads to respiratory failure, intestinal or renal dysfunction, hepatopulmonary syndrome, porto pulmonary hypertension, progressive liver dysfunction or cholestasis and refractory coagulopathy [17]. In our study In 49 cases with good follow up 4 patients (8.1%) had liver transplantation of whom 2 (50%) died. There was cholangitis in 29 (59.1%), GI bleeding in 19 cases (38.7%) and ascites in 24 cases (48.9%) and esophageal varicose in 14 cases (28.5%).

Conclusion

BA is a progressive, idiopathic, fibro-obliterative disease of the extra hepatic biliary tree that presents with biliary obstruction in the neonatal period, and is the most common indication for liver transplantation in children Kasai surgery should be performed as soon as the diagnosis of BA can be made and preferably before 60 days of age. This is because younger age at the time of the Kasai HPE is associated with better outcomes.

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