

# The Management of Biliary Atresia in the Era of Liver Transplantation

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## Abstract

Biliary atresia is the commonest cause of pathological jaundice in infants. The aetiology and pathogenesis are largely unknown despite advances in molecular science. Hepatic portoenterostomy (Kasai operation) remains the primary treatment of choice with a satisfactory cure rate. With the continuing success of paediatric liver transplantation programmes worldwide, many infants with deteriorating liver disease after failed Kasai operations can now be saved by liver transplantation. Here, we discussed the current understanding of biliary atresia and our experience in both the Kasai operation and liver transplantation.

## Key words

Biliary atresia; Kasai operation; Liver transplantation; Risk factors

## Introduction

The hallmark of biliary atresia is the progressive fibrosclerosing obliteration of the extrahepatic biliary system during the first weeks of life. The condition occurs in approximately 1 in 8,000 to 1 in 15,000 live births. Despite early diagnosis and prompt surgical intervention with portoenterostomy to improve biliary drainage, the disease progresses to cirrhosis in many patients. At this end-stage, liver transplantation offers the only hope for long-term survival. The cause and pathogenetic mechanisms of biliary atresia remain largely unknown. Theoretical considerations of the pathogenesis are based largely on epidemiological and clinical features, reported predisposing genetic factors, and the pace of disease progression. Two forms of the disease have been recognised. The "embryonic" type comprises of about 15% of cases and is characterised by cholestasis at

birth with other associated extrahepatic anomalies, such as situs inversus, polysplenia and congenital heart disease.<sup>1</sup> The commoner "perinatal" type occurs in around 85% of cases. In this sub-type, the cholestatic jaundice only manifests after 1 to 2 weeks after birth. There is no associated anomaly in this subtype.

## Pathogenesis

Multiple theories exist for the aetiology of biliary atresia. Hepatotropic and non-hepatotropic viruses have been linked with the disease. In both animal studies and serological evidence, reovirus type 3 and rotavirus have been shown to have the strongest association.<sup>2-4</sup> A direct casual role for viral factors however, is unlikely, since a large epidemiological study did not reveal any seasonal variation of the disease incidence.<sup>5</sup>

Other studies have suggested that there may be a genetic predisposition to the development of the disease. Several HLA haplotypes were shown in a study to be associated with the development of the "perinatal" type of biliary atresia. Furthermore, familial occurrence in twins is reported sporadically.<sup>6-8</sup>

Histologically, inflammatory infiltrate can be seen in the obliterated bile ducts of patients with biliary atresia. The expression of MHC class I molecules, ICAM-1 and CD68 has also been shown to be aberrant.<sup>9-11</sup> These findings

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suggest that host immune factors play a role in the pathogenesis of the disease. Furthermore, gene profiles in livers of infants with biliary atresia show a coordinated activation of genes involved in lymphocyte differentiation, suggesting a potential role of Th-1 like cytokines in disease pathogenesis.<sup>12</sup>

Irrespective of the initiating insult, all infants with biliary atresia share a unique inflammatory and fibrosing obstruction of the extrahepatic biliary system, with pyknosis and necrosis associated with intramural infiltration of mononuclear cells in the bile ducts. Taken together, all these findings suggest that many factors are involved in the genesis of the disease, without a single identifiable biological process driving the pathogenesis.

## Diagnosis

Jaundice in neonates should be investigated to differentiate physiological from pathological jaundice. Hyperbilirubinaemia with a conjugated fraction of more than 20% is abnormal. Other factors such as hepatitis, haematological and metabolic diseases should be excluded. A strong suspicion for biliary atresia is raised if there are also symptoms of pale stool and tea-coloured urine.

Ultrasonography should be performed as a routine since choledochal cysts can easily be demonstrated. Moreover, the presence of a bile-filled gall bladder on ultrasound, although does not exclude implicitly, makes the diagnosis of biliary atresia less likely. The ultrasonographic triangular cord sign, which represents a cone-shaped fibrotic mass, has been found to be a very useful diagnostic feature for biliary atresia.<sup>13</sup> In our unit, hepatobiliary scintigraphy using EHIDA (diethylacetanilido-iminodiacetic acid) with concomitant administration of phenobarbitol is carried out to demonstrate the absence of bile excretion. This method carries a sensitivity and specificity of 95% and 93% respectively. A few papers have recently advocated the use of magnetic resonance (MR) cholangiography in the diagnosis of biliary atresia.<sup>14,15</sup> This has not been widely accepted and in our experience, the sensitivity of current MR cholangiography is not yet high enough to remove the need of other investigations for accurate diagnosis in a small infant.

The gold standard in the diagnosis of biliary atresia remains operative cholangiography. If biliary atresia is confirmed, hepatic portoenterostomy (Kasai operation) can then be performed at the same setting.

## Hepatic Portoenterostomy (Kasai Operation)

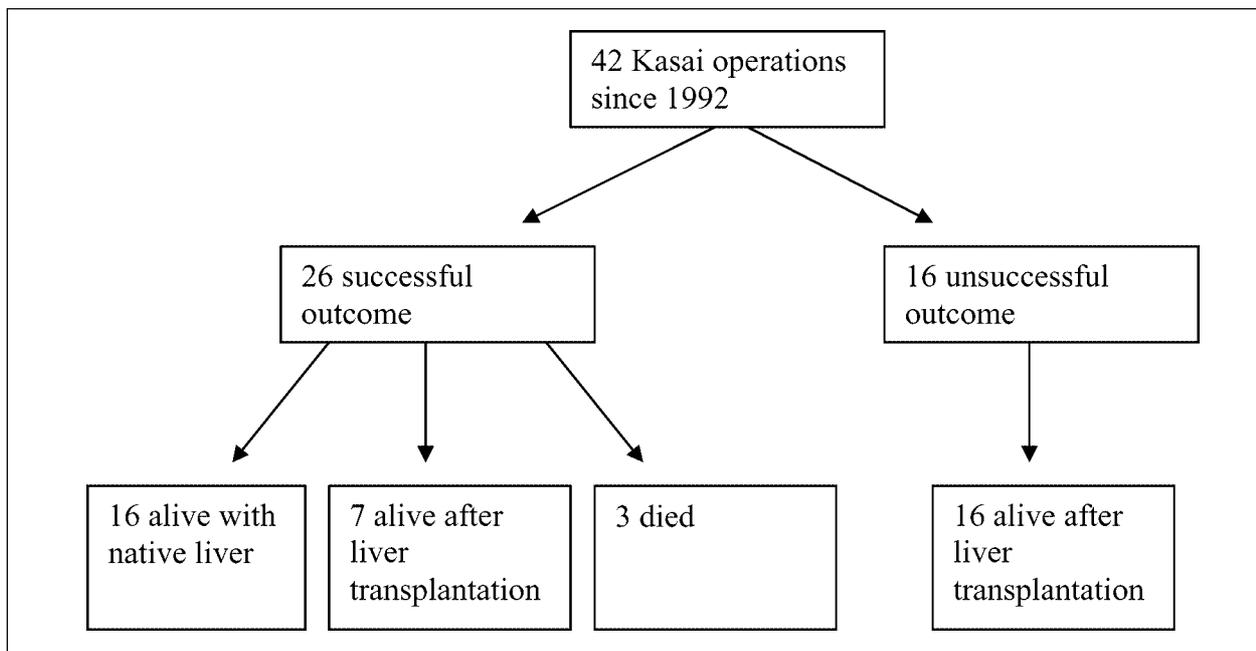
Since its introduction in 1957, hepatic portoenterostomy has become the primary treatment of choice for biliary atresia.<sup>16</sup> The underlying principle of the surgical technique is the en bloc removal of the extrahepatic bile ducts up to the porta hepatis. The exposed liver hilum is then anastomosed to the jejunum using Roux-en-Y. The microscopic biliary structures drain bile into the intestinal conduit, thus relieving the obstruction.

### Outcome

The clinical outcome for patients who underwent Kasai operation depends on the adequacy of bile outflow. Factors thought to influence this include the timing of surgery (it has been shown that there is a significant decrease in successful bile drainage if hepatic portoenterostomy is performed after 60 days of life<sup>17</sup>), the anatomical defect, ductal size of the fibrotic remnant at the porta hepatis, and the experience of the surgical centre. Of these the most important factor that influence the success of portoenterostomy is the caseload of the surgical centre where infants with biliary atresia have their primary surgery.<sup>18</sup> In a prospective study in the United Kingdom and Ireland, it was shown that both survival without liver transplantation and overall survival were significantly better in centres treating more than 5 cases per year. Once centre size was taken into account, no other factor was predictive of survival. Worldwide, results for hepatic portoenterostomy is that approximately one third of cases will have successful long-term survival, one third will need early liver transplantation within a year of the Kasai operation. The remaining third will have a slow deteriorating course, with the need of subsequent transplant.

### HKU Experience

Between January 1980 and January 2003, we have performed 85 hepatic portoenterostomies for biliary atresia with no operative deaths. Forty-two of these were performed after 1992 when the paediatric liver transplantation programme was started. Sixteen patients required early transplantation (38%). The overall actuarial transplant free survival was 68% at 10 years after hepatic portoenterostomy. The outcome of biliary atresia patients after the introduction of liver transplantation programme is shown in Figure 1. Using multivariate analysis, we identified that patients who had poor post-operative bile flow were at risk of developing cholangitis. Furthermore, those who suffered early



**Figure 1** The outcome of children with biliary atresia in the era of liver transplantation.

cholangitis (within 6 months of Kasai operation) were also more likely to have further episodes. The development of cholangitis however, was not found to correlate with a decreased "transplant" free survival, unless the infection was resistant to antibiotic treatment. On the other hand, the post-operative bilirubin level (indicating bile drainage) was found to be the single most important predictor of long-term survival in our series.<sup>19,20</sup>

In the era of laparoscopic surgery, some centres have attempted hepatic portoenterostomy laparoscopically.<sup>21</sup> However we do not advocate replacement of the tried and tested open Kasai's operation with this experimental approach as laparoscopic visualisation and anastomosis at the liver hilum are suboptimal and the likelihood of bile drainage is substantially reduced.

#### **Immunosuppression**

Since host immune factors have been shown to play a role in the pathogenesis of biliary atresia, the use of immunosuppression may dampen the inflammatory response, thus prevent disease progression after the initial portoenterostomy and improve eventual outcome. Although a randomised control trial is required, one retrospective study has suggested that the use of steroids correlates with better bile drainage.<sup>22</sup> In our unit, we prescribe steroids to post-Kasai patients who do not have initial improvement in their biliary obstruction.

#### **Antibiotic Treatment and Prophylaxis**

After Kasai operation, antibiotics is given routinely in most paediatric surgical units. However, long-term use of prophylactic antibiotics has been advocated by some centres. Indeed, a recent study showed that prophylactic oral antibiotics given to patients until the age of three after one episode of cholangitis significantly reduced both the risk of further cholangitis and also the likelihood of subsequent liver transplantation.<sup>23</sup> Although we do not practise long-term prophylactic antibiotics as a routine, we believe in early and aggressive treatment of any suspected cholangitis. We advocate the use of intravenous third generation cephalosporins until a sustained response (resolution of fever and improvement in liver function) is obtained.

#### **Promotion of Biliary Drainage**

Adequate flow of bile reduces the risk of cholangitis and further liver damage. It is therefore important to promote bile drainage. Ursodeoxycholic acid is given to all of our patients who have undergone hepatic portoenterostomies.

#### **Redo-Kasai Operation?**

In the past, many paediatric surgeons have advocated that patients with a failed hepatic portoenterostomy should undergo a reoperation. However, the recent consensus is

that a reoperation is only beneficial in those patients who had initial good bile drainage after the first procedure, as demonstrated by a fall in bilirubin. In the era of successful liver transplantation however, this issue becomes more complex. Since further operation will create excessive adhesions and makes subsequent transplantation technically more difficult, a second hepatic portoenterostomy is undertaken only rarely in very selected cases in our unit.

## Liver Transplantation

More than half of the liver transplantation performed in the paediatric population are patients who have biliary atresia. Although the procedure now carries a very low mortality and morbidity rate, the adoption of transplantation as the primary treatment for biliary atresia is not accepted by most paediatric surgeons because of potential complications from immunosuppression. Nonetheless, transplantation does offer a second line treatment when there is early failure after hepatic portoenterostomy.

### Indications

The indications for liver transplantation in patients with biliary atresia are as follows:

- 1) When hepatic portoenterostomy fails to provide bile drainage and there is evidence of deterioration of liver function.
- 2) When there is developmental delay and inadequate bile drainage.
- 3) Repeated episodes of complications such as variceal bleeding or cholangitis, despite adequate bile drainage.

### HKU Experience

The paediatric liver transplantation programme has been running in our hospital since 1992. Overall forty-two transplants have been performed, with the age range of between 3 months and 12 years (median 12 months). Thirty of these patients (71%) suffered from biliary atresia. Living donor (related or non-related) liver transplant remains the commonest method performed (71%) due to the short supply of cadaveric organs. No donor mortality has been recorded. For the transplant recipients, the overall survival rate is 85% during the mean follow up period of 46 months.<sup>24</sup> This compares favourably with published results from other international centres.<sup>25-29</sup>

### Recent Advances

Reduced size cadaveric liver grafts and living related donor grafts have made available an increased supply of donor organs for the paediatric population. The introduction of newer immunosuppressive agents such as anti-CD25 (IL-2 receptor) antibody means that many post transplant patients can now be maintained on monotherapy alone, thus reducing dramatically the potentially serious complications due to immunosuppression (e.g.) opportunistic infections and malignancy. Further studies in the molecular mechanisms of allograft rejection and tolerance will hopefully result in the better management of these post-transplant patients.

## Conclusion

It has been over 100 years since Thomson first designated biliary atresia as a disease entity.<sup>30</sup> The introduction of hepatic portoenterostomy by Kasai has been an important milestone in the treatment of what used to be a fatal disease. In the era of liver transplantation, more patients can now be saved. Despite this, the understanding of the pathogenesis of biliary atresia remains unclear. Moreover, the disease places enormous emotional and financial burden on patients, families, as well as health workers. The best outcome of treatment is achieved by concentration of surgical expertise at a designated centre.

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