

Long-Term Prognosis and Factors Affecting Biliary Atresia from Experience over A 25 Year Period

Hong-Shiee Lai, MD, PhD; Wei-Jao Chen, MD, PhD; Chiu-Ching Chen, MD; Wen-Tsung Hung, MD, PhD; Mei-Hwei Chang¹, MD

- Background:** The purpose of this study was to delineate the long-term prognosis and factors we have noted in our 25 years of experience treating patients suffering from biliary atresia (BA) who have undergone Kasai's operation.
- Methods:** We studied 141 patients (69 male and 72 female infants) who underwent Kasai's operation at the National Taiwan University Hospital between 1976 and 2000. Factors analyzed included age at time of surgery, postoperative bile flow, frequency of cholangitis, prophylactic long-term oral antibiotics given, and intrahepatic biliary cyst formation.
- Results:** The 5-year and 10-year survival rates for native liver patients were 34.8% (49/141) and 30.5% (43/141). If surgery was performed before the patient was 60 days old, the results were 44.8% (26/58) and 39.7% (23/58). Good bile flow occurred in 115 patients (81.6%) and 88 (62.4%) became jaundice-free. Cholangitis was encountered in 77 patients (54.6%) within the first two postoperative years. Prophylactic oral antibiotics lowered the rate of recurrent cholangitis ($p = 0.011$). Multiple intrahepatic biliary cysts occurred in 11.3% (16/141) of patients, who had a higher mortality rate when compared with the other patients ($p = 0.037$). The factors that had a positive effect include: (1) less than 60 days of age at time of surgery, (2) good bile flow, (3) low frequency of cholangitis, (4) long-term prophylactic antibiotics, and (5) no multiple intrahepatic cyst formation.
- Conclusion:** The long-term survival rate can be improved if Kasai's operation is performed early, there is a detailed dissection producing good bile flow, and long-term prophylactic antibiotics are given to prevent recurrent cholangitis and formation of multiple intrahepatic cysts. (*Chang Gung Med J* 2006;29:234-9)

Key words: biliary atresia, long-term prognosis, cholangitis, antibiotics, intrahepatic cysts.

Introduction

Biliary atresia (BA) is a progressive obliterative cholangiopathy. It has a fatal outcome if left untreated. Since the introduction of hepatic portoenterostomy, a surgical technique to treat non-cor-

rectable BA invented by Dr. Kasai in 1959, there have been encouraging results in treating this disease.⁽¹⁻³⁾ As the incidence of BA is believed to be higher in Asian people than in Caucasians, early diagnosis, surgical treatment and study of prognostic

From the National Taiwan University College of Medicine, Taipei; ¹Department of Surgery and Pediatrics, National Taiwan University Hospital, Taipei.

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Correspondence to: Dr. Hong-Shiee Lai, Department of Surgery, National Taiwan University Hospital. No. 7, Chung-Shan South Road, Taipei, Taiwan 100, R.O.C. Tel.: 886-2-23123456 ext. 5112, 5116; Fax: 886-2-23223870; E-mail: hslai@ha.mc.ntu.edu.tw

factors is very important in any country with a high Asian population.

The surgical approach for correctable BA is by choledocho-enterostomy, similar to the procedure performed for choledochal cysts in the early stages. As for non-correctable BA, surgical intervention increased significantly only after Kasai's operation was reported in 1959. A series of modified Kasai's procedures to increase bile drainage, irrigate the hepatic hilum and prevent ascending cholangitis were subsequently attempted, especially by Japanese groups. However, the original Kasai's hepatic portoenterostomy remains the main choice for surgical intervention at the present time. Factors affecting prognosis postoperatively include: (1) type of BA, (2) age of patient at time of surgery, (3) postoperative bile flow, (4) episodes of postoperative cholangitis, (5) postoperative long-term antibiotics, (6) postoperative steroid administration, (7) intrahepatic biliary cyst formation, and (8) liver cirrhosis.

Kasai's Operation Experience at National Taiwan University Hospital (NTUH)

Since 1968, there have been a total of 216 infants with BA who have undergone Kasai's operation at NTUH. We excluded 21 cases occurring before 1975 because of the incomplete information available. We also excluded 32 cases occurring after 2000 because the follow-up period is only five years. The remaining 163 patients (81 male and 82 female infants) were entered into the study. A further 22 cases were then excluded because of incomplete chart records or follow-up data. The remaining 141 cases (69 male and 72 female infants) were included in this study. They had all undergone a standard Kasai's operation (no modifications) with portal dissection to the lateral sides of the portal vein at a depth of approximately 5 mm with a 45 cm section of jejunum being used as a biliary conduit.

According to the classification schema, 123 cases (87.2%) belonged to type III, 10 cases (7.1%) were type II and eight cases (5.7%) were type I. The average age at surgery was 64.8 ± 12.2 days (range 26 to 298 days). Good bile flow was gained in 115 patients (81.6%) with 88 (62.4%) being jaundice-free when the patients were discharged one month after surgery. Postoperative cholangitis occurred in 108 patients (76.6%) with 31 cases (22.0%) suffering from repeated episodes. A second Kasai's operation

was performed on 24 patients (17.0%), of whom only two survived long-term. Re-laparotomy to release adhesions in the ileus was performed on 14 patients (9.9%).

Long-term prognosis

The long-term prognosis was poor, with a five-year survival rate of 12.5% and a ten-year survival rate of 12.5% for the patients operated on between 1976 and 1980. For those operated on between 1981 and 2000, the five-year survival rate increased to 39.3% and the ten-year survival rate increased to 34.2%.

Age at time of surgery

The long-term survival rate was significantly correlated to the age at which the patient underwent the Kasai's operation. Average ages were 71.1 ± 12.3 days between 1976 and 1983, 74.4 ± 12.2 days between 1984 and 1988, 68.7 ± 8.6 days between 1989 and 1995, and 60.3 ± 10.7 days between 1996 and 2000. Patients less than 60 days old ($n = 58$) at the time of surgery had a five-year survival rate of 44.8% and a ten-year survival rate of 39.7%. Patients between 61 to 90 days old ($n = 39$) 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 ($n = 25$) 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 ($n = 19$) at the time of surgery had a five-year survival rate of 15.8% and a ten-year survival rate of 10.5%.

Postoperative bile flow

Patients with a good postoperative bile flow ($n = 115$) had a five-year survival rate of 42.6% and a ten-year survival rate of 37.4%. The survival rates were zero for patients with a poor postoperative bile flow. Patients who were jaundice-free ($n = 88$) had a significantly higher five-year survival rate of 53.4% and a significantly higher ten-year survival rate of 48.9% ($p < 0.0001$), when compared with patients who had suffered jaundice ($n = 53$) and who had five-year and ten-year survival rates of 3.8% and 0%, respectively.

Episodes of postoperative cholangitis

There were 118 patients who experienced at least one episode of postoperative cholangitis, which

was defined as the presence of recurrent clay-color stools, icteric face, icteric sclera or hyperbilirubinemia.⁽⁴⁾ Their five-year and ten-year survival rates were 41.7% and 36.1%, respectively. Patients suffering more than two postoperative cholangitis episodes ($n = 31$) had five-year and ten-year survival rates of 12.9% and 12.9%, respectively.

Prophylactic long-term antibiotics

From 1997 to 2000, 19 BA patients aged 0 to 2 years, who had had one episode of cholangitis after a Kasai portoenterostomy, received either trimethoprim-sulfamethoxazole (TMP/SMZ) or neomycin orally until the age of three years.⁽⁵⁾ They were assigned randomly into two groups: group one (nine cases) were administered TMP/SMZ (TMP 4 mg/kg/d and SMZ 20 mg/kg/d, divided into two doses), group two (10 cases) were administered neomycin (25 mg/kg/d, qid, four days a week). A further 18 BA patients aged 0 to 2 years, who had had cholangitis but were not prescribed long-term prophylaxis, served as the historical control group. The mean prophylactic periods were 14.6 months for TMP/SMZ and 14.7 months for neomycin. Patients who received prophylaxis, with either TMP/SMZ or neomycin, had lower cholangitis recurrence rates than those in the control group ($p = 0.042$ and 0.011). There was no difference in the cholangitis recurrence rates between the TMP/SMZ and neomycin groups ($p = 0.641$). The survival rates were higher in the TMP/SMZ and neomycin groups than in the control group ($p = 0.09$ and 0.018).

Intrahepatic biliary cyst formation

The 141 patients with BA who were examined for intrahepatic cysts, were followed and examined routinely using abdominal ultrasonography. Twenty-three patients had single intrahepatic cysts and 16 patients had multiple cysts. The incidence of intrahepatic cysts in these patients was 27.6% (39/141) for all kinds of cysts and 11.3% (16/141) for multiple intrahepatic cysts. Of the 16 patients with multiple cysts, 13 (81.3%) had jaundice and 15 (93.8%) had a history of cholangitis before cysts were detected. Image studies showed multiple discrete ovoid or round intrahepatic biliary cysts of various sizes along the biliary trees.⁽⁶⁾ The cysts decreased in size or number in seven patients after antibiotic treatment and disappeared in only one patient. The mortality

rate was higher in patients with multiple cysts than in those with single cysts ($p = 0.037$).

Other factors

The type of BA was considered one of the key factors that affected postoperative prognosis. The long-term survival of those with correctable BA was always better when compared to those with the non-correctable type. Regarding the detailed classification of non-correctable types, it is very sophisticated and difficult to analyze. We were not able to compare the results according to type because of the multiple variations in the classification of non-correctable BA and the limited clarity of the descriptions in the patients' charts. Although there are no detailed comparisons between liver cirrhosis and survival rates in this study, liver cirrhosis is believed to be a negative indicator for long-term survival rate not only in BA patients but also in other kinds of patients. As for postoperative administration of steroids, we believe that steroid administration should play an important role in prevention of early occurrence of cholangitis or biliary tract obstruction. Therefore, we routinely gave steroids to every patient who underwent Kasai's operation. No randomized data is available for comparing the significance of steroid administration to BA patients at our institute.

Discussion

The majority of patients with BA who do not undergo surgery die in early infancy from biliary cirrhosis, hepatic failure and other associated complications. The 3-year overall survival rate is reported to be less than 10% for such patients.⁽⁷⁾

Previous reports state that the patient's age at the time of surgery plays an important role in the long-term prognosis.⁽⁸⁻¹⁰⁾ Patient age at surgical intervention for BA remains a critical issue. Successful portoenterostomy has been reported in infants up to 120 days old.⁽¹¹⁾ However, late age at surgery still contributes to a worse outcome. The result of treatment was also variable among surgeons.⁽¹²⁾ In our study, one third of patients had long-term benefits from Kasai's portoenterostomy.⁽⁴⁾ Overall, long-term survivors of BA can have a good quality of life. Herein, Kasai's operation should be considered as an initial treatment at an early age for all children with BA.

The current status of patients who have survived

for more than ten years after Kasai's operation is good. One study concluded that most long-term survivors whose bilirubin level returned to normal within a short time after surgery could be expected to survive well.⁽¹¹⁾ Our results confirmed that long-term survivors without jaundice could achieve normal growth and life.⁽⁴⁾ Half of our long-term survivors had evidence of liver cirrhosis and portal hypertension; the symptoms were subtle or could be controlled by medical therapies. However, progressive liver insufficiency after puberty was also reported in the late postoperative period.⁽³⁾ Further follow up and management of these problems is indicated.

Cholangitis is a common complication in BA after Kasai's operation and most episodes develop in the first two years of life.⁽¹²⁾ We found that the survival rate was reduced significantly in the first two years postoperatively for patients who suffered repeated episodes of cholangitis.⁽⁴⁾ Recurrent jaundice caused by cholangitis also contributed to mortality and served as an indication for liver transplantation in later life. Prevention of cholangitis is a crucial issue.⁽¹²⁾ At present, our patients are prescribed trimethoprim-sulfamethoxazole or neomycin as prophylactic antibiotics and it appears that this is effective against the recurrence of cholangitis after Kasai's operation.⁽⁶⁾

The precise mechanism by which ascending cholangitis occurs has not been established.⁽⁶⁾ Multifactorial mechanisms should be considered. The prophylactic effects of antibiotics may occur by different pathways: (1) adequate concentrations of antibiotics are excreted from the blood into the cholangioles, and (2) the bacterial concentration is diminished within the bilioenteric conduit. According to Hitch and Lilly,⁽¹³⁾ the presence of antimicrobials (e.g. TMP/SMZ) in bile did not alter the frequency, type or concentration of bacterial growth within the bilioenteric conduit. It was suggested that the efficacy of TMP/SMZ in preventing cholangitis is probably related to the first pathway. However, the organisms most frequently responsible for ascending cholangitis are bacteria that commonly constitute the usual intestinal flora. The most frequently encountered bacterial species with the highest mean concentrations in the jejunostomy fluid are mainly responsible for ascending cholangitis.⁽¹⁴⁾ The prophylactic effect of poorly absorbable neomycin is very likely to be by decreasing the bacterial popula-

tion within the bilioenteric conduit.

We found a high incidence of intrahepatic cysts in patients with BA.⁽⁵⁾ Consistent with previous studies, about a quarter of our patients had at least one cyst detected by sonography.⁽¹⁵⁻¹⁶⁾ Multiple intrahepatic cysts were not uncommon in these patients; of the 39 patients with intrahepatic cysts, 16 (41%) had multiple cysts. The high incidence of multiple cysts in our study may be caused by a longer period of follow-up time and the close sonographic examinations. Since none of these patients had cysts at the time of initial evaluation, we suggest that regular sonographic evaluation is needed for all patients with BA. There were two patients who did not undergo the Kasai procedure but still developed biliary cysts. The biliary cysts might occur, therefore, in patients who have poor biliary drainage and cirrhosis regardless of whether the Kasai procedure is performed.

The pathogenesis of cyst formation is unknown but the following hypotheses have been postulated: (1) cyst formation is secondary to the extrahepatic as well as intrahepatic duct fibro-obliterative process, leading to erosion and ulceration of the biliary epithelium, resulting in bile leakage,⁽⁵⁾ (2) the ongoing inflammatory process results in intrahepatic biliary obstruction, which causes cholangitis and bile cysts,⁽¹⁷⁾ (3) the irregular configuration of the intrahepatic bile ducts becomes exaggerated during the course of cirrhotic changes in the liver, leading to the formation of multicystic dilatation, as in the case of primary biliary cirrhosis,⁽¹⁸⁾ and (4) the ductal plate malformation is one factor causing cyst generation.⁽¹⁹⁾ Ductal plate malformation has been reported in Caroli's disease associated with congenital hepatic fibrosis.

In the majority of patients in this study, the development of multiple cysts was associated with concurrent infections, suggesting that infectious and inflammatory processes played important roles in their development or progression.⁽⁵⁾ After antibiotic treatment, the cysts may regress in size and in number in some cases. Our findings were consistent with those observed by Werlin et al.⁽²⁰⁾ They found that the cysts regressed in size or almost disappeared at times with antibiotics, both with or without external drainage, indicating that if the inflammation subsides, the partial obstruction of the intrahepatic ducts may spontaneously resolve itself.

Liver transplantation is now a legitimate alterna-

tive or complementary method to Kasai's operation.⁽⁷⁾ No patient with jaundice due to poor bile excretion after surgery survived for more than 10 years postoperatively; liver transplantation is definitely indicated. As in our study, most of those who had a poor outcome after undergoing Kasai's operation required transplantation by the time they were three years of age. However, a number of unicteric patients will still require transplantation for problems related to chronic liver disease or repeated cholangitis in adolescence.⁽¹²⁾

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膽道閉鎖病患術後長期預後及影響因素之25年經驗

賴鴻緒 陳維昭 陳秋江 洪文宗 張美惠

- 背景：**由於肝臟捐贈來源之缺乏，葛西式手術在膽道閉鎖症病患仍為必要之手術。本論文重點是探討台大醫院 25 年間，膽道閉鎖症病患接受葛西式手術後，長期預後及影響因素之經驗。
- 方法：**台大醫院於西元 1976 至 2000 年之 25 年間，共有 185 位膽道閉鎖症病患住院，其中 163 位病患接受葛西式手術。扣除資料不齊全之 22 位病患，共有 141 位（69 位男嬰，72 位女嬰）病患納入本文之探討。可能影響預後之因素包括手術年齡、術後膽汁流量、膽道炎發作、長期口服抗生素、及肝內膽道囊腫形成等項目。
- 結果：**未接受葛西式手術之 22 位病患均於 4 歲前死亡。接受葛西式手術之 141 位病患，其 5 年存活率為 34.8% (49/141)，10 年存活率則為 30.5% (43/141)。在 60 天內即接受葛西式手術的病患，則 5 年及 10 年存活率分別為 44.8% (26/58) 及 39.7% (23/58)。術後膽汁流量明顯增加者有 81.6% (115/141)，62.4% (88/141) 出院前已無黃膽現象。共有 77 位病患 (54.6%) 於術後兩年內發生膽道炎。長期給予口服抗生素可有效減低膽道炎復發機率 ($p = 0.011$)。共 11.3% (16/141) 病患有多發性肝內膽道囊腫之形成，其死亡率明顯比其他病患更高 ($p = 0.037$)。
- 討論：**本院 25 年經驗中，膽道閉鎖症病患總長期存活率超過 30%。有意義之影響因素包括：(1) 手術年齡，(2) 術後膽汁流量，(3) 膽道炎發作頻率，(4) 長期口服抗生素，及 (5) 有無多發性肝內膽道囊腫之形成等。膽道閉鎖症病患若能 (1) 於 60 天前接受葛西式手術；(2) 術中剝離肝門出口夠寬廣，使膽汁流量夠多；(3) 當膽道炎發作時即給予長期口服抗生素，避免膽道炎復發及多發性膽道囊腫之形成，將可達到更佳之預後。(長庚醫誌 2006;29:234-9)

關鍵字：膽道閉鎖，長期預後，膽道炎，抗生素，肝內膽道囊腫。