Biliary Atresia in Preterm Infants in Taiwan: A Nationwide Survey

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Objectives To investigate the characteristics of biliary atresia (BA) in preterm infants.

Study design Nationwide screening for BA in Taiwan using an infant stool color card was launched in 2004. We investigated the characteristics of BA in preterm infants using the national stool card registry center database.

Results We identified 197 cases of BA from January 2004 to June 2010. The overall incidence of BA was 1.51 cases per 10 000 live births. The annual incidence of BA per 10 000 live births in term and preterm infants was 1.43 and 2.37 ($P < .05$), respectively. The sensitivity of detecting BA using stool cards before 60 days of age was 92.8% in term, and 96.3% in preterm infants. The Kasai operation before 60 days of age was 68.7% in term, and 44.4% in preterm infants. The jaundice-free rate at 3 months after the Kasai operation among infants with BA was 62.0% in term, and 37.0% in preterm infants ($P = .015$). The 18-month survival rate with native liver was higher in the term infants (72.7%) than that in the preterm infants (50.0%) ($P = .043$).

Conclusion The incidence of BA in preterm infants is more frequent than in term infants. The stool color card is sensitive to detecting BA in preterm infants. Preterm infants with BA were more prone to delayed Kasai operation and had poorer outcome. *(J Pediatr 2013;163:100-3)*.

Biliary atresia (BA) is characterized by progressive inflammation and fibrosis of the extrahepatic biliary ductal system, resulting in bile flow obstruction, persistent cholestasis, and secondary biliary cirrhosis.[1] Without surgery, ongoing injury may lead to cirrhosis, liver failure, and death in the first few years of life. Portoenterostomy (Kasai operation) was introduced in the 1950s. The main purpose of this procedure is to restore biliary flow. The Kasai operation and the development of pediatric liver transplantation (LT) in the 1980s dramatically improved the outcome of patients with BA. BA has been reported worldwide with a wide variety of incidences. The reported incidence of BA shows that the disease is more common in infants from Asian countries than in those from the US and European countries. The incidences (per 10 000 live births) have been reported to be 1.10-1.90 in Taiwan,[2,3] 1.04-1.08 in Japan,[4,5] 0.53 in Canada,[6] 0.65-0.85 in the US,[7-9] 0.71 in Sweden,[10] 0.48-0.59 in the UK,[11,12] 0.51 in France,[13] and 0.50 in The Netherlands.[14]

Previous studies comparing the incidence and outcomes of BA in term and preterm infants were scarce. The aim of this study was to evaluate this concern. Using the national BA registry system data in Taiwan from January 2004 to June 2010, we analyzed the characteristics of all patients with BA in Taiwan and the differences between term and preterm infants.

Methods

Patients were assembled through the Taiwan Infant Stool Color Card Study Group, from January 2004 to June 2010.[3] This national organization consists of 2 parts: the Taiwan Infant Stool Color Card Registry System and the Taiwan Biliary Atresia Study Group. All parents and care givers of babies born in Taiwan since 2004 were given a children's health handbook containing an infant stool color card. Care givers were asked to notify the stool card registry center within 24 hours when abnormal stool color was suspected. Pediatricians in Taiwan routinely evaluated the infant's stool color during hospital visits and were asked to report back to the stool card registry center if abnormal findings were observed. Pediatric surgeons from medical centers in Taiwan encompassed the Taiwan Biliary Atresia Study Group. They were asked to regularly report newly diagnosed cases of BA at least twice a year. The definite diagnosis of BA was made by intraoperative cholangiography. For those who did not receive the Kasai operation initially, the diagnosis was confirmed by histologic and operative findings during the subsequent LT. Gestational age (GA) was categorized as preterm (defined as GA <37 weeks) and term (defined as GA ≥37 weeks). The deferral interval (defined as the duration between the age of symptom onset clay color stool and age at receiving the Kasai operation), LT status, achievement of jaundice-free state (defined as a total serum bilirubin level <2.0 mg/dL with normal stool color) 3 months after the operation,

BA	Biliary atresia
CHD	Congenital heart disease
GA	Gestational age
LT	Liver transplantation

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achievement of 18-month survival with native liver, and other associated congenital anomalies of each subject were dated and analyzed. This study was approved by the Institute Review Board of National Taiwan University Hospital.

Statistical Analyses

Data on the number of live births for both term and preterm infants and their sex were provided from the Bureau of Health Promotion, Department of Health, Taiwan. The annual incidences of BA were calculated by dividing the number of births with BA in each year by the population of live births in the same year from January 2004 to June 2010. The annual incidences were expressed as the number of cases of BA per 10 000 live births. We compared the incidences with 95% CI and OR between term and preterm groups of infants. Logistic regression analyses were used to assess statistically significant variations between groups. Data such as mean age of onset of clay colored stool, mean age at the Kasai operation, mean deferral interval, and mean GA were expressed as mean ± SD and range. The significance of differences among variables was tested using the Mann–Whitney U test. Logistic regression analyses were performed and 95% CI were calculated for the jaundice-free rate in term and preterm groups. The Fisher exact test was used for categorical variables. All statistical analyses were performed using SPSS v. 19.0 (SPSS Inc, Chicago, Illinois).

Results

From January 2004 through June 2010, a total of 197 cases of BA were diagnosed in Taiwan, yielding an annual incidence ranging from 1.12 to 1.84 per 10 000 live births, with an overall incidence of 1.51 per 10 000 live births during the study period; 27 infants were preterm and 170 were term. The incidence of BA was higher in the preterm infants (2.37 per 10 000) compared with the term infants (1.43 per 10 000), and the difference was statistically significant (P = .02, OR 1.65, 95% CI 1.10-2.48). Male-to-female was 18:9 in the preterm group; however, the incidence between sexes was not statistically significant in either term or preterm groups (Table I). The sensitivity of detecting BA using stool color cards before 60 days of age was 92.8% (155 of 167) in the term infants, 96.3% (26 of 27) in the preterm infants without statistical significance between both groups (P = .798) (Table II).

The comparisons of characteristics between the preterm infants with BA and those of the term infants are shown in Table II. Comparing the case numbers of subjects who required LT after Kasai operation and who died during our study period between term and preterm infants, no significant difference were noted (P = .991, .816 respectively). The incidence of major congenital anomalies was higher in the preterm infants compared with the term infants (18.5% vs 4.1%, P = .013). In the preterm group, 5 (18.5%) patients had major extrahepatic congenital anomalies, including congenital heart disease (CHD) in 1, intestinal internal herniation in 1, anal atresia in 1, Down syndrome in 1 and congenital jejunal perforation in 1. In the term group, 7 (4.1%) had major extrahepatic congenital anomalies, including CHD in 6 and intestinal atresia in 2. One term infant had both CHD and intestinal atresia, another term infant had CHD with BA splenic malformation syndrome.

The mean onset age of clay colored stool among the preterm infants with BA was 33.6 ± 12.7 days (14-62 days) compared with 29.7 ± 20.3 days for the term infants (1-114 days); however the difference was not statistically significant (P = .086). The mean age of Kasai operation among the preterm infants was 71.8 ± 27.6 days (22-147 days) compared with 52.9 ± 18.7 days (11-112 days) for the term infants, and the difference was statistically significant (P < .0001). The Kasai operation rate before 60 days of age was significantly lower in the preterm infants (44.4%, 12 of 27) than in the term infants (68.7%, 114 of 166) (P = .025). The mean deferral intervals for the preterm infants and term infants were 38.2 ± 22.8 days and 24.5 ± 15.6 days, respectively, with a significantly longer deferral interval in the preterm infants (P = .001). Among term infants with BA who received the Kasai

Table I. Demographic data of the patients with BA

Characteristics	Number (%)	Rate per 10 000 live births	OR	95% CI	*P* value*
GA					
GA 30 ≤ 37 wk	27 (13.7)	2.37	1.65	1.10-2.48	.02
GA ≥37 wk	170 (86.3)	1.43			
Sex of term patients with BA					
Male	84 (49.4)	1.36	0.91	0.67-1.22	.56
Female	86 (50.6)	1.50			
Sex of preterm patients with BA					
Male	18 (66.7)	2.81	1.56	0.70-3.48	.36
Female	9 (33.3)	1.80			

*Logistic regression.

Table II. Clinical characteristics of the term and preterm infants with BA

Characteristics	Term	Preterm	*P* value
Case no.	170	27	
GA (wk, mean ± SD)		34.3 ± 2.3	
Major congenital anomalies no. (%)	7 (4.1)	5 (18.5)	.013*
Stool color cards sensitivity (%)	155/167 (92.8)	26/27 (96.3)	.798*
Mean age at onset of clay colored stool (days, mean ± SD)	29.7 ± 20.3	33.6 ± 12.7	.086†
Mean corrected age at onset of clay color stool (wk, mean ± SD)		39.2 ± 2.5	
Death no. (%)	13 (7.6)	3 (11.1)	.816*
Received Kasai operation no. (%)	166 (97.6)	27 (100)	.944*
Mean age at Kasai operation (d, mean ± SD)	52.9 ± 18.7	71.8 ± 27.6	<.0001†
Mean corrected age at Kasai operation (weeks, mean ± SD)		44.6 ± 4.0	
Required LT after Kasai operation (%)	49/166 (29.5)	8/27 (29.6)	.991*

*Fisher exact test.
†Mann-Whitney U test.

Table III. Outcomes of term and preterm patients with BA after Kasai operation

	Term	Preterm			
	No. (%)	No. (%)	OR	95% CI	*P* value*
3 mo after operation	166	27			
Jaundice-free	103 (62.0)	10 (37.0)	2.78	1.20-6.45	.015
Jaundice	63 (38.0)	17 (63.0)			
18 mo of age	150	20			
Survive with native liver	109 (72.7)	10 (50)	2.66	1.03-6.86	.043
Received LT & death	35 & 6 (27.3)	7 & 3 (50)			

*Logistic regression.

operation, the jaundice-free rate was 62.0%, compared with 37.0% in the preterm infants, and the difference was statistically significant (P = .015, OR 2.78, 95% CI 1.20-6.45) (Table III). A total of 170 infants diagnosed with BA were born from January 2004 to June 2009. Twenty infants were preterm and 150 were term. In the preterm group, 7 (35.0%) patients received LT, 3 (15.0%) patients died, and 10 (50.0%) patients survived with native liver at 18 months of age. In the term group, 35 (23.3%) patients received LT, 6 (4.0%) patients died, and 109 (72.7%) patients survived with native liver at 18 months of age. The 18-month survival rate with native liver was higher in the term infants (72.7%) compared with the preterm infants (50.0%), and the difference was statistically significant (P = .043, OR 2.66, 95% CI 1.03-6.86) (Table III).

Comparing the preterm infants with and without a jaundice-free status 3 months after surgery, the difference of GA between the 2 groups was not statistically significant (34.0 ± 2.4 vs 34.4 ± 2.3 weeks, P = .69). The mean age at the Kasai operation in preterm patients who were jaundice-free was 63.7 ± 23.0 days compared with 76.6 ± 29.6 days in those who were not jaundice-free; however, the difference was not statistically significant (P = .25). The mean deferral interval in preterm patients who were jaundice-free was 31.3 ± 14.4 days compared with 42.2 ± 26.1 days in those who were not jaundice-free, but the difference was not statistically significant (P = .24).

Discussion

The reported incidence of BA varies widely among different countries and is more common among East Asians and French Polynesians.[15] These differences may reflect genetic predisposing factors. In 1 report, which used the National Health Insurance Database in Taiwan, the overall incidence was 1.46 cases per 10 000 (0.89-1.90 per 10 000) between 1996 and 2003.[2] The incidence in our study was 1.51 cases per 10 000 (1.12-1.84 per 10 000), which is similar to that found previously[2]; however, higher than most reports from Japan[4,5] or Western countries[6-14] except for French Polynesia.[15]

Our study showed that preterm infants had a higher incidence of BA. Infants born prematurely were at 1.65-times the risk of BA compared with infants born at term. Previous studies have also shown that prematurity is an independent risk factor associated with BA.[7,8,10] The association between BA and prematurity is interesting, and the mechanism is currently unclear.[16,17] Furthermore, the relative immaturity of the immune system could lead to chaotic reactions to infectious or other toxic insults, triggering progressive inflammatory responses within the biliary tract.[10]

This study illustrated that the stool color card is sensitive in detecting BA in both preterm and term infants. Preterm infants with BA were more prone to delayed Kasai operation than the term infants (38.2 vs 24.5 days, respectively, P = .001). Fourteen preterm infants had a prolonged deferral interval (≥30 days); causes included 8 whose parents were reluctant to pursue invasive intervention, 3 whose specialists spent longer time excluding other causes of cholestasis, such as total parenteral nutrition and sepsis, 2 with extremely low birth weight, and 2 with major congenital anomalies. The premature nature of these infants may have influenced the family's judgment and cause reluctance to seek medical opinion. These cases indicate that we should educate the parents as well as the medical staff of preterm infants more aggressively and thoroughly to prevent delayed diagnosis and intervention.

The jaundice-free rate after surgery and the 18-month survival rate with native liver was significantly lower in the preterm infants than in term infants (P = .015 and P = .043), thus suggesting BA in preterm infants may result in poorer postoperative prognosis compared with term infants. Although the reasons for this are not entirely clear, it is considered that the immature liver is relatively sensitive to cholestatic injury.[16,17]

Several factors may affect the outcome in infants with BA, and our study showed that prematurity may be a poor prognostic factor. Previous literature indicated delayed Kasai operation may cause poor outcome,[4,18-22] but our study did not replicate this finding in the preterm group. The deferral interval and mean age of Kasai operation showed no significant impact on the jaundice-free status 3 months after surgery in preterm subjects. This study has some limitations. First, it is retrospective with a relatively small sample size. Second, although the study period spans over 6 years, we are aware that longer periods for follow-up of the study groups is needed for further conclusions. ■

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