Epidemiological features of biliary atresia in Taiwan, a national study 1996–2003

Mao-Meng Tiao,* Shang-Shyue Tsai,† Hsin-Wei Kuo,‡ Chao-Long Chen§ and Chun-Yuh Yang‡

Departments of *Pediatrics and §Surgery, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, †Department of Healthcare Administration, I-Shou University, Kaohsiung County, and ‡Institute of Public Health, College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan

See J. Gastroenterol. Hepatol. 2008; 23: 3–4 for Editorial Comment on this article.

Key words
biliary atresia, epidemiology, Taiwan.

Accepted for publication 2 May 2007.

Correspondence
Dr Chun-Yuh Yang, Institute of Public Health, College of Health Sciences, Kaohsiung Medical University, 100 Shih-Chuan 1st RD, Kaohsiung 80708, Taiwan. Email: chunyuh@kmu.edu.tw

Introduction
Biliary atresia (BA) is the leading cause of extrahepatic obstructive jaundice in neonates.1–3 It is now the most common cause of liver transplantation (LT) in children in the developed world,4–11 and portoenterostomy (PE) is used commonly as the first line of treatment.4–12 Untreated BA will result in cirrhosis, hepatic failure and death,4–5 but early diagnosis of BA is difficult with unclear etiology.4–13 Some experts have tried to shed light on the etiology of BA by using epidemiological studies.4–11,14–17 Reported incidence of BA varies widely among different countries. For example, the annual incidence was 1.03–1.08 per 10 000 live births in Japan12,18,19 and 0.70 per 10 000 live births in Australia.4 The annual incidences (per 10 000 live births) reported in Western countries were 3.2 in French Polynesia,7 1.06 in Hawaii,20 0.65–0.85 in the USA,5,9,14 0.71 in the Sweden,17 0.48–0.59 in the UK,15,16 0.51 in metropolitan France10 and 0.50 in the Netherlands.6 The reasons that the incidence rates vary among countries remains unclear, but the differences are possibly related to a combination of factors, including ethnicity, environmental factors and infectious pathogens.

The incidence of BA has not been well investigated in Taiwan. Taiwan implemented the National Health Insurance (NHI) in 1995.21,22 Using the NHI data, we analyzed the epidemiological characteristics and the incidence of BA during a recent 8-year period.

Methods

Data source and definition of cases
In Taiwan, there are 22.66 million people and the land area is 36 179 km², so the population density is 626 persons per km². There are 24 academic medical centers, 72 regional hospitals, and 359 district hospitals.22 We identified BA patients born in the years between January 1996 and December 2003, and their medical records from NHI were followed until December 2004. The NHI databases contained health-care data from 99% of the population receiving health care by the end of 2004 in Taiwan.22 From this database, we identified BA patients on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for BA (751.61) listed as the major or the second diagnosis. Because the discrimination between definite and suspected BA cases is not possible by ICD-9 code, we decided to include only those BA patients who received PE or LT, on the basis of the ICD-9-CM code for portoenterostomy (5137) and
transplantation of liver (5059). Re-do PE cases were identified as those who had claimed twice for PE service. The percentage of PE or LT was calculated by dividing the number of patients who had PE or LT by the total number of BA patients. The diagnostic date was identified as the first time that BA was recorded for the patients.

The annual incidences of BA were calculated by dividing the number of BA births in each year by the population of live births in the same year from January 1996 to December 2003. The annual incidences were expressed as the number of BA cases per 10,000 live births.

Hospital levels, date of birth and gender were collected from the computerized birth certificate data files. Year and month of birth were created from date of birth. Month of birth was collapsed into four seasons: winter (December–February), spring (March–May), summer (June–August) and autumn (September–November).

Statistical analysis

We analyzed the data using SAS statistical software (Version 8.2; SAS Institute, Cary, NC, USA). Data were expressed as mean ± standard deviation (SD) or median (range). The significance of differences among continuous variables was tested using the Mann–Whitney U-test. The difference in seasonal distribution, and the difference in female-to-male ratio were measured using Pearson χ² test. A linear time trend analysis was performed to analyze the change of annual incidence over years. Patient survival was assessed using Kaplan–Meier method and compared between groups using the log–rank test. Survival with native liver was analyzed using time from birth until either death or LT. The analysis of overall survival used time from birth to death. A P < 0.05 was considered statistically significant.

Results

Demography of patients

Among 878 cases with ICD-9 code of BA, a total of 327 BA cases received PE or LT from January 1996 to December 2003 in Taiwan. The number of cases per year varied between 29 and 53, with the mean caseload of 41 new BA patients per year. The annual incidence ranged from 0.89 to 1.90 per 10,000 live births, with the overall incidence of 1.46 per 10,000 live births during the 1996–2003 period (Table 1). The female-to-male ratio was 174:153, among the 2,246,924 live births including 1,074,046 female and 1,172,878 male. The BA incidence was higher for girls (1.62 per 10,000) than for boys (1.30 per 10,000), but the difference was not statistically significant (P = 0.714, OR 1.04, 95% CI 0.84–1.29).

Months and seasonal distribution

During the 8-year study period, the incidence of BA was not significantly different over the months (P = 0.673). The incidences in each season were 1.41 per 10,000 live births in spring, 1.47 in summer, 1.47 in autumn and 1.48 in winter (P = 0.990). A linear time trend analysis was performed and the estimated slope for annual incidence (rate of increase per year was 0.14 per 10,000 live births) was significant (P = 0.006). It is interesting that the peak incidence (1.90 per 10,000 live births) occurred in 2002, especially in that summer (2.68 per 10,000 live births; Fig. 1), accompanying with Taiwan’s dengue fever epidemic in 2002.23,24

Diagnostic age and hospital level distribution

The diagnostic age was 51.8 ± 40.1 days old. Most of the cases (74.0%, n = 242) were diagnosed before 60 days old, and 7.0%
Epidemiology of biliary atresia

M-M Tiao et al.

Portoenterostomy

The PE procedure was done in 91.7% (300 of 327) of BA cases. Most of the PE (69.3%, 208 of 300) were done before the age of 60 days old, and 9.3% (28 of 300) were done after 90 days old (Fig. 2). The percentage of patients undergoing PE was 96.0% in medical center (288 of 300) and 4.0% in regional hospitals (12 of 300). The date of PE was not significantly different between those with LT and those without LT or LT (n = 57) and those without LT (n = 243; 56.4 ± 36.1 days vs 57.2 ± 44.4 days, P = 0.916). Patients with re-do PE (five male and eight female) had a median interval between the first PE and the second PE of 198 days (7–749 days). The percentage of patients receiving PE was not significantly different between during 1999–2003 and during 1996–1998 (212 of 232 vs 88 of 95, P = 0.708, OR 0.84, 95% CI 0.34–2.07).

Transplantation

Liver transplant was performed in 25.7% (84 of 327) patients (M : F = 40:44) with the median age of 1.13 years old (0.44–6.42 years old). Among them, 57 patients had undergone a previous PE and 27 cases had not. The diagnostic age did not differ significantly between those with LT and those without LT (54.2 ± 37.2 days vs 50.9 ± 41.1 days, P = 0.552). The LT rate was not significantly different in those who underwent PE in regional hospitals (three of 12) and in medical center (54 of 288; OR 1.44, 95% CI 0.38–5.52, P = 0.705). The percentage of patients receiving LT was significantly higher during 1999–2003 than during 1996–1998 (73 of 232 vs 11 of 95, P < 0.001, OR 3.51, 95% CI 1.76–6.97).

Outcome

The 5-year overall survival rate was significantly higher than the survival rate of native liver (70.2% vs 45.1%, P < 0.001; Fig. 3). The 5-year overall survival rate in those who received LT was much higher than those who did not receive LT (91.1% vs 62.8%, P < 0.001). The 5-year survival rate with native liver was higher in those who underwent PE before 60 days old than those after (53.7% vs 36.7%, P = 0.017). The 5-year overall survival rate was not different between those who underwent PE before 60 days old and those after (69.5% vs 63.6%, P = 0.572). The 5-year overall survival rate during 1999–2003 was higher than that during 1996–1998 (74.8% vs 61.1%, P = 0.014).

Discussion

Biliary atresia is more common among Asians. It occurs in approximately 1.25 of 10 000 live births in Asian countries and 0.56 of 10 000 live births in European countries. Shim et al. also reported wide variation in the incidence of BA among Chinese (3 per 10 000), Filipino (2 per 10 000) and Caucasian (0 per 10 000) infants. In Chen’s report, the annual incidence was 3.7 per 10 000 in Taiwan, but the study included less than one-third of all live births (119 973 of 474 600) from 2002 to 2003. In our study, Taiwan had a BA incidence of 1.46 per 10 000 live births between 1996 and 2003, higher than that (1.03–1.04 per 10 000) reported in Japan. Our incidence was also higher than most of those reported in Western countries (0.51–1.06 per 10 000), except that reported in French Polynesia (3.2 per 10 000). The advantage of the current study is that the data are from the entire population of all children born in one country during a defined period of time and the quality of the NHI registers has been analyzed previously. One limitation in our study is that, due to the coding methodology, it is not possible to distinguish definite from suspected BA cases. The design of the national databases used in the study does not allow access to the chart review of individual patients. We decided to make a more conservative estimation to identify only those cases receiving PE or LT as definite BA cases. It has been reported that the percentage of BA cases without PE or LT was 11.9% (n = 22) among 185 cases in Taiwan, 6.1% (n = 7) among 114 cases in the UK, 3.8% (n = 32)
among 852 cases in Japan,27 3.3% (n = 15) among 461 cases in France28 and 2.2% (n = 2) among 93 cases in the UK and Ireland.15 In Chen’s report, the percentage of BA cases without PE or LT was 3.4% (n = 1) among 29 cases in Taiwan.29 If we added 11.9% (n = 44) as BA cases without PE or LT, then our total cases would be 371, and the annual incidence of BA would be 1.65 per 10 000 live births. Conversely, the misdiagnosis rate of BA for those receiving PE has been reported to be 9.5% (n = 4) among 42 cases in Taiwan29 and 1.3% (n = 6) among 461 cases in France.10,28 In Chen’s report, the misdiagnosis rate of BA for those receiving PE was reported to be 3.4% (n = 1) among 29 cases in Taiwan.21 If we supposed a 9.5% misdiagnosis rate for BA cases with PE, the annual incidence would drop to 1.32 per 10 000 live births. So we can estimate that the annual incidence is between 1.32 and 1.65 per 10 000 live births. This would still be the second-highest annual incidence in the world.

Racial differences in the incidence of BA may be consistent with genetic predisposition;30,31 however, if the incidence is influenced only by genetic differences, the incidence of BA should be constant throughout the year.18 Therefore, differences in incidence throughout the year hint that environmental or infectious factors may play an important role in the pathogenesis of BA. Infectious causation would seem to be a strong possibility in many BA cases.13,17,32–40 There is no monthly or seasonal variation in the incidence of BA according to the reports in Michigan (USA), Sweden, France and England.12,10,17,33 However, different conclusions have been reported.13,9,14,19 In our study, there was no significant difference between seasons. It is interesting that the peak incidence (1.90 per 10 000 live births) occurred in 2002, especially in that summer (2.68 per 10 000 live births), accompanying with Taiwan’s dengue fever epidemic in 2002.23,24 It is supposed that viral infection outbreaks remained potential candidates as causes of BA.17 The dengue fever epidemic could have influenced pregnancies and the fetus, inducing the higher BA incidence in 2002. We believe the findings from our study indicate that further investigation of the association between BA and environmental agents such as dengue virus is needed.

We also observed a slight and significant increase in the incidence of BA during 1996–2003. The possible explanation for this slight increase was the reporting system of the Taiwan Biliary Atresia Study Group established in 1999. It recruited 21 major medical centers and hospitals to report on newly diagnosed BA cases twice a year. With this reporting system, physicians may have been more alert about this disease and more BA cases would therefore be identified. Besides, the number of pediatric gastroenterologists has more than doubled from 45 persons in 1996 to 110 persons in 2003 in Taiwan.41 The more professionals specialized in the field of pediatric gastroenterologist, the more BA cases could be identified earlier and receive appropriate treatment.

Our data show that, consistent with previous studies,12,13,16,25,35,36,40,42,43 those who had a delayed PE (after 60 days old) had a worse 5-year native liver survival rate. We also found the percentage of cases receiving LT during 1999–2003 was higher than that during 1996–1998 and this was accompanied with a better 5-year overall survival rate. This means that the management for BA has been improving, especially for the LT management. In Taiwan, the source of organ donation for LT is still limited due to cultural attitudes. This is an area for which public education can lead to better outcomes in the future.

In conclusion, among areas for which published data are available, Taiwanese children have the second-highest incidence of BA reported in world literature. There is a slight increase in the incidence during the 8-year study period. Viral infection outbreaks remain a potential candidate as a cause of BA. The management for BA has been improving, especially for LT management.

Acknowledgment
This study was supported in part by grant (CMRPG850281) from the Chang Gung Memorial Hospital.

References
Epidemiology of biliary atresia


21 Cheng TM. Taiwan’s new national health insurance program: genesis and experience so far. Health Aff. 2003; 22: 61–76.


