Incidence of Biliary Atresia and Timing of Hepatoportoenterostomy in the United States

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Objective To evaluate the incidence, trends, seasonality, and age at the time of hepatoportoenterostomy (Kasai procedure) for biliary atresia in the US.

Study design The triennial Health Cost and Utilization Project–Kids' Inpatient Database for 1997-2012 was used to perform a retrospective analysis of biliary atresia in the US. Infants aged <1 year of age with a diagnosis of biliary atresia who underwent a Kasai procedure were included. Nationwide infant population data were used to calculate incidence and evaluate trends. Age at the time of the Kasai procedure and the seasonality of biliary atresia were evaluated as well.

Results The incidence of biliary atresia in the US was 4.47 per 100 000 and was higher in females (risk ratio [RR], 1.43; 95% CI, 1.27-1.62), Asian/Pacific Islanders (RR, 1.89; 95% CI, 1.44-2.47), and blacks (RR, 1.30; 95% CI, 1.06-1.58) compared with whites. The incidence of biliary atresia increased by an average of 7.9% per year from 1997 to 2012 ($P < .001$). The median age at the time of the Kasai procedure was 63 days, with no improvement over the study period ($P = .64$). There was no evidence of seasonality ($P = .69$).

Conclusion The incidence of biliary atresia has increased over the past 15 years, with the median age at the time of the Kasai procedure now outside the optimal window. Implementation of systematic screening measures for biliary atresia in the US are needed. *(J Pediatr 2017;187:253-7).*

Biliary atresia is a progressive destructive disorder of the intrahepatic and extrahepatic bile ducts. Left untreated, biliary atresia is fatal, making it the leading indication for liver transplantation in children.[1] There is no medical treatment for biliary atresia; surgical treatment with hepatoportoenterostomy (Kasai procedure) is the gold standard.[2,3] Successful establishment of bile flow with the Kasai procedure is directly linked to an increase in patient survival with native liver.[4] Among infants who undergo the Kasai procedure within 60 days of life, 57%-90% will have successful reestablishment of bile flow, but the success rate drops to <20% if the procedure is performed after 90 days of life.[2,5-7] This time-sensitive success rate makes the infant's age at the time of surgery crucial to optimize outcomes and decrease short- and long-term morbidity and mortality,[2,3] and underscores the importance of early diagnosis of biliary atresia.

The pathogenesis of biliary atresia is not well understood, but owing to a reported seasonality of the disease in some population studies, is thought to be linked to a viral illness that stimulates the inflammatory obliteration of the bile ducts. Studies using a rotavirus-induced murine model of biliary atresia have shown that maternal vaccination against rotavirus can prevent biliary atresia in newborn mouse pups.[8,9] Lin et al found a significant drop in the incidence of biliary atresia in Taiwan between 2004-2006 and 2007-2009 (1.76 cases vs 1.23 cases per 10 000 live births).[10] The trend toward decreasing biliary atresia in Taiwan is hypothesized to be linked to implementation of a nationwide rotavirus vaccination.[10]

The impact, if any, of rotavirus vaccination on the incidence of biliary atresia in the US is unclear. The American Academy of Pediatrics (AAP) technical report on newborn screening for biliary atresia noted that the incidence and prevalence of biliary atresia are current key questions.[11]

We conducted the present study to determine the incidence of biliary atresia in the US, and to evaluate whether that incidence is decreasing, similar to what has been seen in other countries. Secondary aims were to determine whether early identification of biliary atresia is improving in the US, resulting in performance of the Kasai procedure during the optimal window of the first 60 days of life, and to evaluate whether there is seasonality to the incidence of biliary atresia in the US.

AAP	American Academy of Pediatrics
HCUP-KID	Healthcare Cost and Utilization Project-Kids' Inpatient Database
ICD-9	*International Statistical Classification of Diseases and Related Health Problems, Ninth Revision*
RR	Risk ratio

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Methods

Data on biliary atresia hospitalizations in children aged <1 year were obtained from the triennial Healthcare Cost and Utilization Project–Kids' Inpatient Database (HCUP-KID), sponsored by the Agency for Healthcare Research and Quality. The HCUP-KID is the largest publicly available nationwide inpatient database devoted to children in the US. National total population data by age and year also are available from the HCUP-KID, to allow estimates of incidence. The database used for the present study consisted of a stratified random sample across 6 years: 1997, 2000, 2003, 2006, 2009, and 2012. It contains approximately 3 million pediatric inpatient records per year from 4100 hospitals collected between 1997 and 2012. The database includes data from between 22 and 44 states, depending on the year. Each record in the database includes up to 25 diagnoses (15 before 2009) and 15 procedural codes based on the *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* (ICD-9). The HCUP-KID assigns an individual-level population weight that allows for estimation of national case incidences and trends. The age in days at time of admission is reported for infants aged <1 year between 1997 and 2009.[12]

Variable Definition

Case selection was performed by searching the database for children aged <1 year with the ICD-9 diagnostic code for biliary atresia (751.61) and for the procedure code for the Kasai hepatoportoenterostomy procedure (51.37). Criteria for inclusion in the study were the diagnosis code for biliary atresia and receipt of the Kasai hepatoportoenterostomy during hospitalization. In an effort to identify only incident cases of biliary atresia and to avoid duplicating subjects in the database, subjects identified as having undergone liver transplantation during hospitalization (50.5X, 998.1) were excluded.

The population denominator data by year were obtained from the HCUP-KID.[13] Demographic data included race, sex, and geographic region. The analysis of race/ethnicity was grouped into white, black, Hispanic, Asian/Pacific Islander, Native American, and other, based on race classification provided in the HCUP-KID. The hospital region was classified as Northeast, Midwest, South, or West.

Statistical Analyses

The overall and yearly incidences of biliary atresia were calculated by dividing the nationally weighted number of hospital admissions that met the study criteria by the total number of reported infants in the US population for the respective years. The estimated population of infants (ie, children aged <1 year) is reported by the HCUP-KID.[14] The trends in biliary atresia were tested using the Cochrane-Armitage test of trend. Patient age at the time of Kasai hepatoportoenterostomy was calculated using age in days at the time of admission to the hospital as reported by the HCUP-KID. The age in days data represented only a subset of subjects, because available data were limited to the years 1997-2009. The age distribution at the time of Kasai hepatoportoenterostomy was found to be skewed and is reported as median (IQR). The Kruskal-Wallis test was used to test differences in age at the time of Kasai hepatoportoenterostomy across the years.

The seasonality of biliary atresia was tested using the X11 procedure, an adaptation of the US Census Bureau's X-11 Seasonal Adjustment program.[15,16] A combination of 2 tests of seasonality—the stable seasonality test and moving seasonality test—was used. The stable seasonality test is a 1-way ANOVA on the detrended series with months as the factor. The moving seasonality test is a 2-way analysis that uses both months and years.[15] The analyses were performed using the provided population weights as recommended by HCUP-KID documentation.[12] Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina), and all statistical tests were performed at a significance level of $\alpha = 0.05$. This study was reviewed and approved by the Uniformed Services University of the Health Sciences Institutional Review Board.

Results

A total of 1057 nationally weighted cases of biliary atresia recorded in the US between 1997 and 2012 met the study cirteria. The overall incidence of biliary atresia in the US in 1997-2012 was 4.47 per 100 000 children age <1 year.

The incidence of biliary atresia was higher in females than in males (5.36 per 100 000 vs 3.74 per 100 000; risk ratio [RR], 1.43; 95% CI, 1.27-1.62) (**Table**). Asian/Pacific Islanders had a higher incidence of biliary atresia compared with whites (7.55 per 100 000 vs 4.00 per 100 000; RR, 1.89; 95% CI, 1.44-2.47) or with blacks (5.18 per 100 000; RR, 1.30; 95% CI, 1.06-1.58). There was no significant difference in the incidence of biliary atresia across US regions ($P = .29$).

The incidence of biliary atresia increased significantly over the study period, from 2.85 cases per 100 000 in 1997 to 5.55

Table. Demographics of biliary atresia in the US, 1997-2012

Variables	No. of biliary atresia cases	Incidence per 100 000 children	RR (95% CI)	*P* value
Sex				<.001
Female	610	5.36	1.43 (1.27-1.62)	
Male	446	3.74	Reference	
Race				<.001
White	403	4.00	Reference	
Black	131	5.18	1.30 (1.06-1.58)	<.001
Hispanic	174	4.43	1.11 (0.93-1.32)	.26
Asian/Pacific Islander	612	7.55	1.89 (1.44-2.47)	<.001
Native American	2	1.67	0.42 (0.10-1.67)	.22
Other	79	7.72	1.93 (1.52-2.46)	<.001
Unreported race	207	4.25		
Region				.29
Northeast	192	4.85		
Midwest	245	4.80		
South	365	4.20		
West	255	4.56		