Biliary Atresia: The Canadian Experience

Richard A. Schreiber, MD, FRCP(C), Collin C. Barker, MSc(Epid), MD, FRCP(C), Eve A. Roberts, MD, FRCP(C), Steven R. Martin, MD, FRCP(C), Fernando Alvarez, MD, Lesley Smith, MD, FRCP(C), J. Decker Butzner, MD, FRCP(C), Iwona Wrobel, MD, FRCP(C), David Mack, MD, FRCP(C), Stanley Moroz, MD, FRCP(C), Mohsin Rashid, MD, FRCP(C), Rabin Persad, MD, FRCP(C), Dominique Levesque, MD, FRCP(C), Herbert Brill, MD, FRCP(C), Garth Bruce, MD, FRCP(C), Jeff Critch, MD, FRCP(C): Canadian Pediatric Hepatology Research Group

Objective To determine the outcomes of Canadian children with biliary atresia.

Study design Health records of infants born in Canada between January 1, 1985 and December 31, 1995 (ERA I) and between January 1, 1996 and December 31, 2002 (ERA II) who were diagnosed with biliary atresia at a university center were reviewed.

Results 349 patients were identified. Median patient age at time of the Kasai operation was 55 days. Median age at last follow-up was 70 months. The 4-year patient survival rate was 81% (ERA I = 74%; ERA II = 82%; P = not significant [NS]). Kaplan-Meier survival curves for patients undergoing the Kasai operation at age ≤30, 31 to 90, and >90 days showed 49%, 36%, and 23%, respectively, were alive with their native liver at 4 years ($P < .0001$). This difference continued through 10 years. The 2- and 4-year post-Kasai operation native liver survival rates were 47% and 35% for ERA I and 46% and 39% for ERA II (P = NS). A total of 210 patients (60%) underwent liver transplantation; the 4-year transplantation survival rate was 82% (ERA I = 83%, ERA II = 82%; P = NS).

Conclusions This is the largest outcome series of North American children with biliary atresia at a time when liver transplantation was available. Results in each era were similar. Late referral remains problematic; policies to ensure timely diagnosis are required. Nevertheless, outcomes in Canada are comparable to those reported elsewhere. *(J Pediatr 2007;151:659-65)*

Biliary atresia is an idiopathic neonatal obstructive cholangiopathy characterized by a progressive fibrosclerosing obliteration of the large bile ducts that presents uniquely in the first months of life.[1-3] It is the leading cause of end-stage liver disease in children and the most common indication for liver transplantation in the pediatric population. Two clinical phenotypes of biliary atresia have been recognized.[2,3] Most patients with biliary atresia (70% to 95%) have no associated extrahepatic congenital abnormalities and are classified as having "classical" biliary atresia. The remaining cases present in association with 1 or more extrahepatic congenital anomalies, including polysplenia, portal vein abnormalities, intestinal malrotation, abdominal situs inversus, and congenital heart disease. These patients are classified as having *biliary atresia splenic malformation syndrome* (BASM) and may represent a unique subset with differing pathogenesis and timing of disease onset (earlier) from the "classical" phenotype.[4]

Regardless of phenotype, no curative therapy for biliary atresia exists. Sequential surgical management with an initial hepatic portoenterostomy (Kasai operation) followed by liver transplantation for those patients who progress to end-stage liver disease is considered the current standard of care.

Many of the published reports on the outcome for patients with biliary atresia have been based on single-center experiences of limited sample size or from data completed at a time before the era when pediatric liver transplantation became readily and routinely available as a treatment option.[5-9] More recently, large national European and Asian studies have examined, from a country-wide perspective, the patterns of referral, diag-

BASM Biliary atresia splenic malformation syndrome

From the Departments of Pediatrics: the University of British Columbia, Vancouver, British Columbia (R.S., C.C.), University of Toronto, Toronto, Ontario (E.R.), University of Montreal, Montreal, Quebec (S. Martin, F.A.), University of Alberta, Edmonton, Alberta (L.S.), University of Calgary, Calgary, Alberta (J.B., I.W.), University of Ottawa, Ottawa, Ontario (D.M.), University of Manitoba, Winnipeg, Manitoba (S. Moroz), Dalhousie University, Halifax, Nova Scotia (M.R.), McMaster University, Hamilton, Ontario (R.P.), McGill University, Montreal, Quebec (D.L., H.B.), University of Saskatchewan, Saskatoon, Saskatchewan (G.B.), and Memorial University, St. John's, Newfoundland, Canada (J.C.).

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Reprint requests: Dr. Richard Schreiber, Clinical Professor of Pediatrics, University of British Columbia, Division of Gastroenterology, BC Children's Hospital, Room K4-200, 4480 Oak Street, Vancouver, BC, Canada V6H 3V4. E-mail: rschreiber@cw.bc.ca.

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nostic evaluation, management, and outcomes of children with biliary atresia in the era of pediatric liver transplantation.[10-14]

In Canada, national health insurance policies guarantee universal access to health care for all citizens regardless of age or economic status. Moreover, pediatric tertiary care is already highly centralized, with complex cases managed almost exclusively at university-based pediatric hospital centers. Herein we report the overall outcomes of Canadian children with biliary atresia throughout the study period (1986 to 2002), assess the prognosis for patients managed in an earlier era (1986 to 1995) compared with those treated more recently (1996 to 2002), and compare our results with those of other large national studies.

METHODS

The medical records of 355 patients with biliary atresia born between January 1, 1985 and December 31, 2002 who were diagnosed and followed at 1 of 12 Canadian university-based pediatric tertiary care institutions were reviewed (Appendix; available at www.jpeds.com). Biliary atresia cases were identified through the health records department at each institution using the standard national numerical coding systems for the diagnosis of biliary atresia or the surgical intervention of Kasai operation. Data collected from each chart included unique patient identifier; date of birth; sex; ethnicity; birth weight; date of onset of jaundice; date of referral; imaging studies done; liver histology; presence of the BASM phenotype; presence of any of the following: polysplenia, portal vein anomalies, intestinal malrotation, abdominal situs inversus, or congenital heart disease; whether a Kasai operation was performed; date of Kasai operation; postoperative medications; time to clear jaundice; whether liver transplantation was performed; date of transplantation; date of last follow-up; and final outcome. All data were recorded onto a uniform spreadsheet by the investigator at each center and then, after eliminating patient identifiers, electronically transferred to the central registry at BC Children's Hospital. The database was critically reassessed by a single investigator (R.S.) to ensure accuracy and completeness and then further anonymized. Duplicate cases (eg, when a patient had transferred care from one center to another) were eliminated.

The diagnosis of biliary atresia was confirmed based on standard clinical, biochemical, radiologic, histological, and operative findings. Six cases were excluded because the diagnostic criteria could not be fully satisfied due to missing reports. Thus, a total of 349 patients were included in the study. Due to the retrospective nature of this study, complete data collection was not possible in all cases.

The study patients were first analyzed as a single group. The group was then divided into 2 cohorts, an earlier group (ERA I) born between January 1, 1985 and December 31, 1995 and a later group (ERA II) born between January 1, 1996 and December 31, 2002, to compare our data with those from other published national studies. Survival curves were calculated according to the Kaplan-Meier method, with overall patient survival defined as starting at birth and ending at death or last follow-up; liver transplantation survival beginning at transplantation and ending at death or last follow-up; and native liver survival starting at birth and ending at death, transplantation, or last follow-up. Results are expressed as calculated survival rate with 95% confidence intervals. The proportional hazard ratio for the Kaplan-Meier curves was verified graphically. Univariate analysis was done using rank-sum and log-rank tests. Comparisons of the 2 eras were made to check whether outcomes changed between them. Median and ranges were measured for the various time variables, because the data had a nonparametric distribution. *T* tests and χ^2 tests were used to compare descriptive measures and categorical data between the 2 eras. All significance tests were 2-tailed, with α fixed at 0.05. All statistical analyses were done with Stata version 8.1 (StataCorp, College Station, TX). The study was approved by each university's and hospital's ethical review board.

RESULTS

Patient Characteristics and Evaluation

A total of 349 Canadian children with biliary atresia were identified over the entire study period, including 199 cases in ERA I and 150 cases in ERA II (Table; Figure 1). The female-to-male ratio was 1.4:1. The overall median age of the study patients at last follow-up was 5.8 years (range, 2 months to 19.5 years); median age was 8.8 years (range, 2 months to 19 years) in ERA I and 3.8 years (range, 2 months to 9.6 years) in ERA II. In terms of ethnicity, the study group was 59% Caucasian, 14% Asian, 9% Native American, 4% African American, and 14% other race. The diagnostic evaluation included abdominal sonography (in 89% of cases), hepatobiliary scintigraphy (in 84% of cases), and preoperative liver biopsy (in 78% of cases). The BASM phenotype was diagnosed in 27 patients, representing 14% of the reported cases.

The medical management and survival outcomes of the patients for ERA I and ERA II are summarized in Figure 1. According to the live birth rates during the study period as reported by Statistics Canada, the estimated incidence of biliary atresia in Canada throughout the study period was approximately 1:19,065, or 5.25/100,000, live births (range, 4.91 to 5.63/100,000); that in ERA I was 1:21,348, or 4.68/100,000 (range, 4.65 to 4.97/100,000), and that in ERA II was 1:16,035, or 6.23/100,000 (range, 5.95 to 6.55/100,000).[15]

Referral Age and Age at Kasai Operation or Transplantation

The median patient age at the time of the initial referral to a tertiary care pediatric hospital center was 55 days (range, 1 to 191 days). There was no significant difference in the median referral age between ERA I and ERA II (Table). The Kasai operation was performed in 312 children (89%); the median age at surgery was 65 days (range, 6 to 200 days);