Medical Status of 219 Children with Biliary Atresia Surviving Long-Term with Their Native Livers: Results from a North American Multicenter Consortium

Vicky Lee Ng, MD[1], Barbara H. Haber, MD[2], John C. Magee, MD[3], Alexander Miethke, MD[4], Karen F. Murray, MD[5], Sonia Michail, MD[6], Saul J. Karpen, MD[7,8], Nanda Kerkar, MD[6,9], Jean P. Molleston, MD[10], Rene Romero, MD[8], Philip Rosenthal, MD[11], Kathleen B. Schwarz, MD[12], Benjamin L. Shneider, MD[13], Yumirle P. Turmelle, MD[14], Estella M. Alonso, MD[15], Averell H. Sherker, MD[16], and Ronald J. Sokol, MD[17], on behalf of the Childhood Liver Disease Research and Education Network (CHiLDREN)*

Objectives To examine the medical status of children with biliary atresia (BA) with their native livers after hepatoportoenterostomy (HPE) surgery.

Study design The Childhood Liver Disease Research and Education Network database was utilized to examine subjects with BA living with their native livers 5 or more years after HPE and to describe the prevalence of subjects with BA with an "ideal" outcome, defined as no clinical evidence of chronic liver disease, normal liver biochemical indices (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, platelet count, total bilirubin, international normalized ratio, and albumin), and normal health-related quality of life 5 or more years after HPE.

Results Children with BA (n = 219; 43% male) with median age 9.7 years were studied. Median age at HPE was 56 (range 7-125) days. Median age- and sex-adjusted height and weight z-scores at 5-year follow-up were 0.487 (IQR −0.27 to 1.02) and 0.00 (IQR −0.74 to 0.70), respectively. During the 12 preceding months, cholangitis and bone fractures occurred in 17% and 5.5%, respectively. Health-related quality of life was reported normal by 53% of patients. However, only 1.8% met the study definition of "ideal" outcome. Individual tests of liver synthetic function (total bilirubin, albumin, and international normalized ratio) were normal in 75%, 85%, and 73% of the study cohort.

Conclusion Cholangitis and fractures in long-term survivors underscore the importance of ongoing medical surveillance. Over 98% of this North American cohort of subjects with BA living with native livers 5 or more years after HPE have clinical or biochemical evidence of chronic liver disease. *(J Pediatr 2014;165:539-46)*.

Biliary atresia (BA) is a progressive fibro-obliterative cholangiopathy presenting only in infancy with a prevalence ranging from 1 in 5000 to 18 000 newborns.[1] Hepatoportoenterostomy (HPE; the Kasai procedure) provides a means of relieving extrahepatic biliary obstruction and permitting bile flow but is not a curative procedure.[2,3] Despite HPE being performed in a timely fashion, liver transplantation (LT) is ultimately required for the majority of patients during childhood.[4,5] Although single center[6-8] and multicenter[9-11] characterizations of the health status and medical outcomes in patients with BA who have undergone LT are available, the long-term outcomes in older children with BA living with their native livers have not been examined in detail

Alb	Albumin	CLD	Chronic liver disease
ALT	Alanine aminotransferase	GGT	γ-glutamyl transpeptidase
AST	Aspartate aminotransferase	HPE	Hepatoportoenterostomy
BA	Biliary atresia	HRQOL	Health-related quality of life
BASIC	Biliary Atresia Study of Infants and Children	INR	International normalized ratio
		LT	Liver transplantation
ChiLDREN	Childhood Liver Disease Research and Education Network	PedsQL	Pediatric Quality of Life Inventory
		PHT	Portal hypertension
		TB	Total bilirubin

From the [1]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; [2]Division of Gastroenterology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA; [3]Department of Surgery, University of Michigan Medical School, Ann Arbor, MI; [4]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [5]Hepatobiliary Program, Seattle Children's Hospital and University of Washington, Seattle, WA; [6]Department of Gastroenterology and Nutrition, Children's Hospital Los Angeles, Keck School of Medicine University of Southern California, Los Angeles, CA; [7]Texas Children's Hospital, Houston, TX; [8]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [9]Division of Pediatric Hepatology, Mount Sinai School of Medicine, New York, NY; [10]Pediatric Gastroenterology, Hepatology, and Nutrition, Riley Hospital for Children, Indiana University, Indianapolis, IN; [11]Pediatrics Gastroenterology, Hepatology, and Nutrition, University of California San Francisco Benioff Children's Hospital, University of California, San Francisco, CA; [12]Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins Medical Institutions, Baltimore, MD; [13]Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Hospital Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, PA; [14]Division of Gastroenterology and Nutrition, Washington University, St. Louis, MO; [15]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Ann and Robert H. Lurie Children's Hospital and Northwestern University, Chicago, IL; [16]Liver Diseases Research Branch, NIDDK, NIH, Bethesda, MD; and [17]Department of Gastroenterology, Hepatology, and Nutrition, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO

*List of members of CHiLDREN is available at www.jpeds.com (**Appendix**).

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in large patient populations and are limited to small single-center retrospective experiences.[12-18] Progression to chronic liver disease (CLD) was avoided in only 11% of 244 ten-year survivors of HPE performed at King's College Hospital over the 12-year period of 1979 to 1991.[19] Detailed information from a contemporary multicenter population of older subjects with BA surviving with their native livers currently does not exist, and would aid clinicians in providing important and generalizable information to families about school-aged children with BA.

Established in 2002, the Childhood Liver Disease Research and Education Network (ChiLDREN; originally known as the Biliary Atresia Research Consortium) is a National Institute of Diabetes, Digestive, and Kidney Diseases/National Institute of Health-funded cooperative research consortium at 15 clinical sites in the US and Canada with the goal of understanding the etiology, pathogenesis, course, and outcomes of BA as well as other pediatric cholestatic conditions. Herein, the objectives of this cross-sectional study were to utilize enrollment data available within the ChiLDREN database to characterize the medical status of a multicenter cohort of subjects with BA who were 5 years of age or greater at time of study enrollment and still living with their native livers following HPE and to identify the percentage of subjects with BA who have no clinical findings of CLD, normal health-related quality of life (HRQOL), and normal laboratory indices at least 5 years after HPE.

Methods

The Biliary Atresia Study of Infants and Children (BASIC) is one of the ongoing longitudinal studies within ChiLDREN with a specific aim to determine natural history and outcomes of older nontransplanted children with BA. Patient inclusion criteria for the BASIC protocol were subjects with: (1) a confirmed diagnosis of BA determined by chart review, including review of pertinent diagnostic biopsy reports, radiologic reports, and surgical reports; (2) age ≥6 months; (3) either native livers or post-LT; and (4) a parent/guardian willing to provide informed consent (and, when appropriate, the subject is willing to assent). For this present cross-sectional analysis, subjects were identified from the BASIC database with patient age between 5 and 17.99 years at time of BASIC enrollment, and at least 1 year of follow-up at a ChiLDREN study site in the year preceding BASIC enrollment. Importantly, to reduce the bias of assessing patients with BA with severe disease who were unlikely to have long-term survival with native liver, subjects were excluded from this analysis if they were already listed for LT at time of BASIC enrollment.

All of the participating ChiLDREN centers had institutional review board and/or research ethics board approval for this study.[20] Written informed consent was obtained from parents and/or guardians, and assent obtained from subjects age 7 years and older.

At BASIC entry, demographic, clinical, and laboratory data were collected, physical examinations performed, and past medical histories (including medical events in the previous 12 months abstracted from the medical record) were recorded. Definitions and specific criteria for complications of CLD were standardized within the ChiLDREN protocol. Diagnosis of cholangitis required presence of fever of >38°C without other obvious clinical source of infection; new onset of acholic stools, right upper quadrant pain or tenderness; and both elevation of direct bilirubin by 25% and at least >1 mg/dL above previous baseline; however, positive bacterial or fungal culture (of blood or liver) was not required. Hepatopulmonary syndrome required documentation of hypoxemia with pulse oximetry (transcutaneous saturation) levels of less than 94% and evidence of intrapulmonary shunting by contrast echocardiography with agitated saline.[21]

Data collected included sex, race, date of birth, ethnicity, date of HPE, associated congenital malformations,[22] and medications. Physical examination findings included weight, height, head circumference, anthropometry, liver, and spleen size on examination. Laboratory indices included complete blood count with differential, international normalized ratio (INR), liver biochemical results, and basic metabolic panel. Growth data were expressed as z-scores relative to published age-adjusted normative values.[23]

Given the healthcare complexities involved in the care of a child with chronic medical condition, an overall framework for outcome assessment based on a hierarchy of outcome measures can provide caregivers and parents a measure of the observed vs expected health status of the individual patient.[24] Understanding the extent to which the health of the infant with BA is restored to normal following HPE is important as a benchmark by which future interventions can be measured. For the purposes of this present analysis, "ideal" clinical outcome in BA (criteria variables provided in **Table I**) as derived by the ChiLDREN investigators was defined as the combination of: (1) normal liver biochemical test values; (2) absence of selected clinical complications of CLD (in the entire life of the subject); (3) absence of the need for additional medications specifically indicated for underlying liver disease; and (4) normal self-reported HRQOL. These criteria were dichotomized to facilitate a "yes" or "no" answer from review of the BASIC data collection forms. Normal liver laboratory values were defined as serum total bilirubin (TB) ≤1.5 mg/dL, aspartate aminotransferase (AST) ≤45 IU/L, alanine aminotransferase (ALT) ≤40 IU/L, γ-glutamyl transpeptidase (GGT) ≤ 55 U/L, albumin (Alb) ≥3.3 g/dL, INR ≤1.3, and platelet count >150 × 10^9/L. Absence of clinical CLD was defined as no report of ascites, hepatopulmonary syndrome, variceal bleeding, and/or pathological bone fractures, in conjunction with the presence of age-adjusted growth (both weight and height) z-scores >−2.0, and no reported use of cholangitis prophylactic antibiotics. Normal HRQOL was defined as Pediatric Quality of Life Inventory (PedsQL) 4.0 generic core scale total score scores >69.7 for child self-report or >65.4 for parent proxy—threshold scores representing 1 SD below the population mean.[25,26] Given the paucity of