CLINICAL—BILIARY

Cardiac Structural and Functional Alterations in Infants and Children With Biliary Atresia, Listed for Liver Transplantation

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BACKGROUND & AIMS: Cirrhotic liver diseases are associated with abnormalities in cardiac geometry and function in adults (cirrhotic cardiomyopathy) but rarely explored in cirrhotic infants or children. We proposed that features of cirrhotic cardiomyopathy are present in infants with cirrhosis due to biliary atresia (BA) as early as the time of evaluation for liver transplant and will correlate with mortality and postoperative morbidity. **METHODS:** Two-dimensional echocardiography (2DE) of infants with BA (n = 40; median age, 8 months), listed for transplantation at the Texas Children's Hospital from 2004 to 2010, were reviewed and compared with age- and sex-matched infants without cardiac or liver disease (controls). Length of stay and correlation with 2DE results were assessed. **RESULTS:** Compared with controls, children with BA had significant increases in multiple 2DE parameters, notably left ventricle wall thickness (23% increase), left ventricular (LV) mass indexed to body surface area (51% increase), and LV shortening fraction (8% increase). Overall, features of cirrhotic cardiomyopathy were observed in most infants (29/40; 72%); 17 had hyperdynamic contractility, and 24 had altered LV geometry. After liver transplantation (33), infants with abnormal 2DE results had longer stays in the intensive care unit (median, 6 vs 4 days) and the hospital (21 vs 11 days) compared with infants who had normal 2DE reports. On univariate analysis, the length of hospital stay correlated with LV mass index. **CONCLUSIONS: Cardiomyopathy is a prevalent condition in infants with end-stage cirrhotic liver disease due to BA (>70%). This underrecognized condition likely contributes to the prolongation of posttransplant hospitalization.**

Keywords: Pediatric; Heart; Liver Disease; Morbidity; Cholestasis; Remodeling.

Cardiac dysfunction in cirrhosis (cirrhotic cardiomyopathy [CC]) is characterized by multiple alterations in cardiac conduction, physiology, and structure.[1,2] In general, there are 5 key components of CC: left ventricular (LV) and septal hypertrophy, impaired diastolic LV relaxation, hyperdynamic LV contractility, prolonged QTc interval, and an attenuated cardiovascular response to stressors (eg, hypovolemia, septic mediators, and pharmacologic inotropic medications).[3] The development of cardiomyopathy in adults with cirrhosis increases their risk of development of exercise fatigue, hepatorenal syndrome, postoperative complications, dysrhythmias, and death.[4–6] In addition, several features of CC subside after transplant, suggesting that in the setting of cirrhosis, the heart responds to signals from the diseased liver in ways that, if prolonged, may prove detrimental to the patient.[7,8] The timeline and underlying etiologies of CC are essentially unknown.

There are few informative animal models of CC; some have been explored using bile duct ligation or xenobiotic-induced biliary cirrhosis.[9–13] In these models, there is a common feature of a rapid development of cardiac hypertrophy and altered function, including an impaired inotropic response. Within 3 weeks of inducing biliary fibrosis in mice, there is a marked hypertrophic and hyperdynamic myocardial response (2-fold increase in cardiac mass, 20-fold increase in β-myosin heavy chain RNA, and ~35% increase in LV ejection fraction) along with altered cardiac metabolic pathways, all suggesting that the mouse heart rapidly and profoundly responds to biliary cirrhosis with features reminiscent of CC in humans.[8,13] The underlying mechanisms of altered cardiac structure and function are under investigation, but it appears to relate to the rapid and stereotyped response of the heart to circulating factors including cytokines[14] and retained biliary constituents (eg, bile acids).[15–19]

The development of clinically relevant alterations (hypertrophy and hyperdynamic contractility) in the mouse heart within a few weeks of damage to the biliary tract suggests that these (mal)adaptive pathways may be present early in the course of cirrhosis in humans. If so, infants with biliary atresia (BA), a disease of biliary cir-

Abbreviations used in this paper: BA, biliary atresia; CC, cirrhotic cardiomyopathy; 2DE, 2-dimensional echocardiography; GGT, γ-glutamyltransferase; ICU, intensive care unit; LOS, length of stay; LV, left ventricular; LVM, left ventricular mass; LVMI, left ventricular mass index; PELD, Pediatric End-Stage Liver Disease; PICU, pediatric intensive care unit; RWT, relative wall thickness.

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rhosis that begins soon after birth, would be the ideal group to study. However, few cardiac evaluations in this susceptible population have been reported,[20,21] and it is unknown if structural, functional, and electrophysiologic abnormalities even exist in infants with BA. The rapid development of cirrhosis in infants with BA, often by 3 months of age, suggests that a detailed cardiac evaluation in this population would shed light on the potential development of CC and perhaps if any associated cardiac phenotypes correlate with pretransplant and posttransplant survival, as seen in adults.[22] Thus, the goal of the current study was to characterize the structural, functional, and physiologic characteristics of hearts of infants and children awaiting a transplant due to the principal indication for transplantation in children: BA. Moreover, we sought to determine if there were potential correlates of cardiac findings with outcomes, namely, survival and postoperative length of stay (LOS).

Subjects and Methods

Subjects

All children evaluated for liver transplant at the Texas Children's Hospital (n = 138) between January 2004 and June 2010 were considered potential enrollees for the study. Given the variety of diagnoses, we sought to focus on those with the most prevalent diagnosis who also have a high rate of mortality on the wait-list: those with BA. Care and evaluation have been relatively uniform during this period at the institution, including the performance of 2-dimensional echocardiography (2DE) in nearly all. During this period, 48 infants with BA were evaluated and listed for transplant; 42 were younger than 2 years of age. This young BA cohort (cirrhotic, "failed Kasai") is at high risk for death awaiting a transplant.[23,24] The study plan of enrollees and 2DE evaluations is noted in Figure 1. Of the 42 infants, only 2 listed infants with BA did not undergo 2DE before transplant. Thus, a total of 40 infants with BA, 33 of who underwent a transplant and 7 who died before transplant, form the core group evaluated in this study. Cardiac Autopsy was performed on 3 of the 7 children who died prior to transplantation (See Supplementary Methods section). This research protocol was approved by the Baylor College of Medicine Institutional Review Board.

Echocardiography

2DEs were routinely performed during liver transplant candidacy evaluation at the Cardiology Clinic at Texas Children's Hospital. No infants were found with serious structural heart disease. 2DEs of age- and sex-matched children without cardiac or liver disease (n = 30) who presented to the Cardiology Clinic were randomly selected as controls. 2DE reports were evaluated for key parameters determining LV geometry: LV free wall thickness in diastole, LV free wall thickness in systole, septal thickness in diastole, and septal thickness in systole as well as LV end-diastolic and end-systolic dimensions. LV mass (LVM) was calculated using the formula by Devereux et al[25] according to American Society of Echocardiography guidelines and indexed to both length$^{2.7}$ (g/m) and body surface area (g/m^2). For characterization of cardiac geometry, LVM was indexed to body surface area to minimize the potential for overdiagnosis of LV hypertrophy in this age group.[26,27] Relative wall thickness (RWT), defined as the ratio of LV wall thickness to LV end-diastolic dimension, was calculated using the following standard formula: RWT = (Septal Thickness in Diastole + LV Free Wall Thickness in Diastole)/LV End Diastolic. LV geometry was then subdivided into 4 groups based on LV mass index (LVMI) (g/m^2) and RWT (cm) values[28]: (1) normal geometry (normal LVMI and RWT), (2) concentric remodeling (normal LVMI and increased RWT), (3) concentric hypertrophy (increased LVMI and RWT),

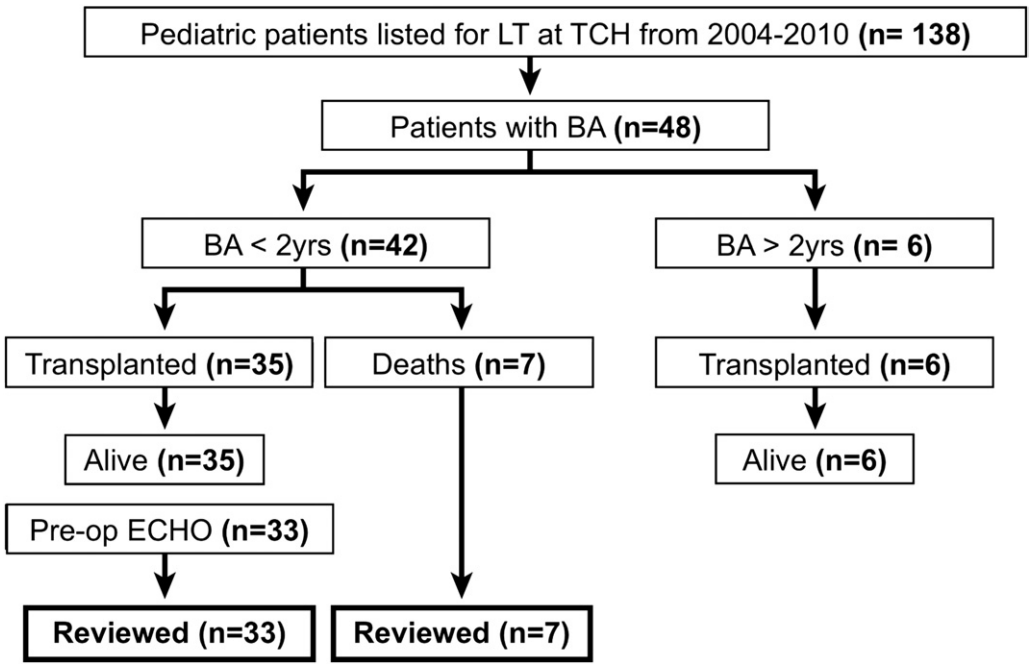

Figure 1. Patients with BA selected for study. The flowchart depicts patients listed for liver transplant (LT) during the study period of January 2004 to June 2010. TCH, Texas Children's Hospital.