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Portal and centrilobular hepatic fibrosis in Fontan circulation and clinical outcomes

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BACKGROUND: The Fontan operation redirects venous blood flow directly to the pulmonary circulation in subjects with single ventricle anatomy. Congestive hepatopathy and cirrhosis have been described in subjects with Fontan circulation, but the prevalence of and predictors for liver disease remain unknown.
METHODS: We performed a retrospective study of liver histopathology in Fontan subjects who had liver biopsy or autopsy. All specimens were graded using a pre-determined protocol. Additional data were collected through chart review. Among 68 subjects, specimens were obtained at a median age of 23.2 years (range 5.0 to 52.7 years). Median time since Fontan was 18.1 years (range 1.2 to 32.7 years).
RESULTS: Centrilobular fibrosis was seen in every specimen, with 41.2% showing Grade 4 centrilobular fibrosis. Portal fibrosis was seen in 82.3% of specimens, with 14.7% showing cirrhosis. Megamitochondria were seen in 58.8% of specimens. Centrilobular fibrosis grade was greater in those with a dominant left or right ventricle than in those with a combined right and left systemic ventricle ($p = 0.008$). Portal fibrosis grade correlated with alkaline phosphatase ($p = 0.04$) and mode of biopsy ($p = 0.02$). Neither centrilobular fibrosis nor portal fibrosis grade was predictive of transplant-free survival or overall survival.
CONCLUSIONS: Individuals with Fontan physiology have a high prevalence of hepatic fibrosis. Signs and symptoms of liver disease did not predict histopathologic findings. Few risk factors for advanced disease were identified. Histopathology findings did not predict transplant-free survival. The role of liver biopsy in this population remains uncertain.
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The Fontan procedure diverts systemic venous blood in patients with univentricular hearts directly into the pulmonary circulation, resulting in near normalization of systemic oxygen saturation and ventricular volume load, but depressed cardiac output and increased central venous pressure.[1,2] Long-term survivors of the Fontan operation encounter complications such as arrhythmia, heart failure, congestive hepatopathy, plastic bronchitis and protein-losing enteropathy.[3] Few predictors of poor outcomes in individuals with Fontan circulation have been identified.[4]

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Liver disease is increasingly reported in adults with Fontan circulation.[5,6] Fibrosis in inflammatory liver diseases is centered on the portal triad and leads to portal hypertension, whereas hemodynamic derangements, such as those seen in congestive heart failure, generally result in centrilobular fibrosis. Although systems exist for grading portal fibrosis,[7–10] there is no standardized system for grading the centrilobular fibrosis characteristic of congestive liver disease.[11] Because clinicians remain generally reluctant to pursue tissue diagnosis, histopathology data on liver disease in the Fontan population remain sparse.

In this study, we aimed to determine the prevalence of histopathologic liver disease after Fontan palliation and to identify correlations between histopathologic findings and hemodynamic measurements, biochemical markers or clinical history.

Methods

Study design

This was a retrospective study approved by the Boston Children's Hospital institutional review board. Individuals with prior Fontan surgery were identified from the Boston Children's Hospital cardiac database, and pathology slides for those in whom liver biopsy or autopsy had been performed after Fontan surgery were obtained for review. Biopsies or autopsies were primarily performed at Boston Children's Hospital or Brigham and Women's Hospital. Biopsies performed elsewhere were included if the original slides were available for review.

Data collected from chart review included: demographics; cardiac anatomy data; surgical interventions; and viral hepatitis serologies. Additional data collected if obtained within 6 months of liver biopsy included: hemodynamics; imaging parameters of cardiac function; peak VO_2 on cardiopulmonary exercise testing; complete blood count; international normalized ratio in subjects not taking warfarin; basic metabolic panel; aspartate aminotransferase; alanine aminotransferase; gamma glutamyltranspeptidase; alkaline phosphatase; albumin; total protein; and total bilirubin. Physical examination and abdominal imaging performed within 1 year of liver biopsy were reviewed for documentation of splenomegaly, or coarse or heterogeneous liver appearance.

Clinical complications recorded included: arrhythmias, defined as sustained tachyarrhythmia or bradyarrhythmia requiring treatment; thromboembolic events after Fontan completion; protein-losing enteropathy, confirmed by stool α_1-anti-trypsin and hypoalbuminemia; plastic bronchitis; clinically significant ascites, defined as symptomatic ascites or ascites requiring diuresis or paracentesis; esophageal varices on imaging or endoscopy; or congestive heart failure, defined as requiring hospital admission for intravenous diuretics or inotropic agents.

All liver biopsies were performed for clinical indications. Slides stained with hematoxylin and eosin and Masson's trichrome were evaluated by a single pathologist (A.R.P.) blinded to initial assessment. The METAVIR fibrosis staging system was used to grade portal fibrosis: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa; F3 = numerous septa without cirrhosis; and F4 = cirrhosis. An analogous semi-quantitative scoring system, ranging from 0 to 4, was utilized for grading central fibrosis: 0 = no pericellular fibrosis; 1 = circumferentially focal or uneven pericellular fibrosis up to a radial length of 3 hepatocytes; 2 = circumferentially uniform pericellular fibrosis up to a radial length of 3 hepatocytes; 3 = circumferentially uneven or complete pericellular fibrosis beyond a radial length of 3 hepatocytes; and 4 = confluent fibrosis with parenchymal replacement. Scores of 3 or 4 out of 4 were regarded as advanced fibrosis. Core fragmentation, sinusoidal dilation, steatosis, inflammation, hepatocellular damage and necrosis were graded on a semi-quantitative scale of 0 to 4. Bridging fibrosis (characterized as central–central, portal–portal or central–portal), cholestasis, lipofuscin and megamitochondria were graded as present or absent.

Statistical analysis

Patient variables are reported as median with interquartile range for continuous variables and count with percentage of total for nominal variables. To examine the association of patient variables with portal and centrilobular fibrosis stages, subjects were divided into those with no or mild fibrosis (Grade 0 to 2) and those with marked fibrosis (Grade 3 or 4). Wilcoxon's rank-sum test, Fisher's exact test and/or unpaired Student's *t*-test were performed as appropriate to determine whether each variable differed significantly between the 2 groups. A 2-sided $p < 0.05$ was considered statistically significant. For transplant-free survival analysis, patient data for those without an adverse outcome were censored at their last clinical contact. Kaplan–Meier survival curves were generated to assess time from biopsy, excluding autopsies, to death or heart transplant for those with no or mild portal fibrosis versus those with marked portal fibrosis, and for those with no or mild centrilobular fibrosis versus those with marked centrilobular fibrosis. Log-rank tests were used to compare transplant-free survival curves between groups, and *p*-values using Cox regression were calculated to adjust for a potential confounding impact of age at biopsy. Logistic regression analysis was performed using a dependent variable of death within 3 years. All data analysis and figures were performed with SAS for Windows 9.3 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

Seventy-four subjects with Fontan circulation were identified who had liver histology. Six of these were excluded for: biopsy pre-dating Fontan surgery (1); original slides/paraffin blocks not available (4); or inadequate stain quality (1). In the end, 68 subjects (36 male) were reviewed. Of these, 5 had biopsy on more than 1 occasion; only the first biopsy was used for analysis.

Table 1 summarizes the subject characteristics. Fifty-nine had liver biopsy and 9 had autopsy. Median age at initial Fontan completion was 5.0 years (range 0.7 to 39.0 years). Six subjects underwent conversion from an atriopulmonary anastomosis to a lateral tunnel or extracardiac conduit before liver biopsy.

Most subjects (72%) were negative for hepatitis C (HCV) antibody. Ten had known chronic HCV infection. None underwent treatment before liver biopsy; 5 were treated afterward. Of 9 subjects not tested for HCV, only 2 had surgery before July 1992. The others had no risk factors for HCV infection.