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Original contribution

Prevalence and characterization of fibrosis in surveillance liver biopsies of patients with Fontan circulation☆,☆☆

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Summary The Fontan operation is a widely used palliative procedure in patients with single-ventricle anatomy that results in liver injury. As timely identification of liver fibrosis may result in management changes to Fontan patients, the aim of our study was to identify clinically meaningful semi quantitative/quantitative pathologic parameters for biopsy assessment. We performed a retrospective review of 74 liver needle biopsies from Fontan patients. Fibrosis was assessed using quantitative % collagen deposition by Sirius red image analysis, METAVIR, congestive hepatic fibrosis score, sinusoidal fibrosis score, and sinusoidal dilation score. Contemporaneous laboratory, hemodynamic, and ultrasound data were collected. Centrilobular and peri sinusoidal fibrosis was observed in all cases, with 39.2% high grade. Portal fibrosis was observed in 93.2%, with 36.2% high-grade (METAVIR F3-F4). Cirrhosis was observed in 5.4%. % Collagen deposition was increased over control tissue ($P < .001$) and correlated with time from Fontan ($r = 0.3$, $P = .009$) and prothrombin time ($r = 0.25$, $P = .034$). Mildly elevated prothrombin time/international normalized ratio was the only measure of liver function consistently associated with multiple high-grade fibrosis scores (METAVIR $P = .046$, sinusoidal fibrosis $P = .018$). Abnormal liver echotexture on ultrasound was associated with high-grade congestive hepatic fibrosis score ($P = .03$). Pathologic gradings and %CD correlated with each other ($r = 0.48$-0.8, $P < .001$). Hepatic fibrosis in Fontan patients in our study is universally present, appears to

Abbreviations: CHOP, The Children's Hospital of Philadelphia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltranspeptidase; AFP, α-fetoprotein; PT, prothrombin time; INR, international normalized ratio; IVC, inferior vena cava; %CD, percent collagen deposition; CHFS, congestive hepatic fibrosis score; ALC, absolute lymphoctye count; ANC, absolute neutrophil count; AP, alkaline phosphatase; BNP, B natriuretic peptide; WBC, white blood cells.

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be time dependent, and correlates with few laboratory measurements of liver function. Careful assessment of needle liver biopsies lends a more meaningful measure of liver fibrosis in the Fontan patient than clinical and laboratory data, allowing for appropriate changes to patient management.

1. Introduction

The Fontan operation is a widely used palliative procedure in patients with single-ventricle type of congenital heart disease. In the absence of a ventricle delivering blood to the lungs, the Fontan procedure channels central venous blood directly to the pulmonary arteries. This allows for separation of the pulmonary and systemic circulations and improves systemic oxygen saturation. However, the Fontan operation leads to increased central venous (inferior and superior vena cava) pressures, which can result in chronic venous congestion, low cardiac output and altered end-organ perfusion. The unintended consequence of the Fontan physiology in long-term survivors leads to a number of complications, which include hepatic fibrosis/cirrhosis, protein-losing enteropathy, plastic bronchitis, arrhythmia and heart failure [1,2].

Liver fibrosis in patients with Fontan physiology presents significant management challenges and may impact long-term clinical outcome [3,4]. Potential causes of liver fibrosis in children with single-ventricle physiology include injury present as a neonate from shock or hypoxemia, perioperative insults from multiple operations that precede the completion of the Fontan circuit itself, and injury from late complications of chronic venous congestion and altered circulation [5-7]. Severe hepatic fibrosis or cirrhosis may shorten life expectancy, impact candidacy for heart transplantation, and increases the risk of hepatocellular carcinoma [3,8-11].

The course of hepatic changes resulting from the Fontan circulation has not been clearly described, and it has been challenging to characterize this aspect of end-organ damage in long-term survivors. Clinical and laboratory data do not provide for an accurate assessment of fibrosis, and no single measure has been adopted as the standard for post-Fontan liver fibrosis evaluation. Non-invasive techniques such as ultrasound-based transient elastography or magnetic resonance elastography have not been validated in this population and need further studies [12]. Thus far, liver biopsy is the best standard for assessment of hepatic fibrosis. However, there are no widely accepted pathologic fibrosis scoring systems or guidelines to suggest the significance of the observed fibrosis in this population, as most were devised to evaluate chronic hepatitis and thus may not be applicable to Fontan-associated liver disease. Quantitative assessment of collagen deposition and/or a more specific pathologic scoring system, which characterizes comprehensive total fibrosis including centrilobular and portal changes, would be of value.

Timely identification and characterization of liver histopathology can play an important role in the clinical management of patients with Fontan circulation. An agreed upon standard for characterization of liver fibrosis in this population will allow for a "gold standard" towards which to compare non-invasive assessments and can also be used as a benchmark to evaluate efficacy of potential therapeutic strategies [13]. The purpose of our study is to describe the patterns of liver fibrosis after Fontan operation, their optimal histological assessment, and their association with clinical measures in order to develop meaningful parameters for surveillance in this growing young population at risk for liver disease.

2. Materials and methods

A retrospective review of clinical data was performed with approval by The Children's Hospital of Philadelphia Institutional Review Board. Data were collected as part of a clinical surveillance program offered to patients with a Fontan circulation through the Single Ventricle Survivorship Program at Children's Hospital of Philadelphia. Following a multidisciplinary symposium held at our institution, consensus was achieved on the importance of offering liver biopsy evaluation to all patients who are 10 years or greater following Fontan operation [5]. This would allow for individual patient knowledge concerning the state of their liver as well as offer the opportunity for optimization of the Fontan circulation. Patients were included if they had undergone a liver biopsy between 2009 and 2014. Evaluation of patients in the program included clinical examination, laboratory data, cardiac catheterization, and liver biopsy. All liver tissue specimens were obtained through a percutaneous approach, not a transjugular approach. This was done in order to attempt to obtain a more representative sample of overall liver fibrosis and avoid sampling bias of obtaining selected tissue from the perivascular region, which may theoretically be more affected by venous congestion.

All liver biopsies were obtained as part of routine screening in patients who were predominantly asymptomatic from the cardiovascular perspective and were outpatient and highly functional (New York Heart Association Class I or II). Demographics and clinical data (time from Fontan operation to biopsy and Fontan type) were collected by chart review. The findings of ascites, caput medusa, jaundice, spider angioma, peripheral edema, and organomegaly were included if noted in the patient's physical exam within 3 months of the liver biopsy. Laboratory data were reviewed and included if obtained within 3 months of the liver biopsy (usually immediately preceding), including aspartate aminotransferase, alanine aminotransferase (ALT), total protein, albumin, alkaline phosphatase, γ-glutamyl transferase (GGT),