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Original article

A clinical review of congenital hepatic fibrosis diagnosed in adulthood: presentation, complications, and outcomes

Lauren Loeb[a], Jason Lewis[b], Zhongwei Peng[c], Michael G. Heckman[c], Raouf Nakhleh[b], Andrew P. Keaveny[d,*]

[a] Department of Internal Medicine, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA
[b] Department of Pathology, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA
[c] Clinical Trials and Biostatistics, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA
[d] Department of Transplantation, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA

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ABSTRACT

Introduction and Objectives: Congenital hepatic fibrosis (CHF) is a rare condition characterized by biliary tract changes and a geographic pattern of liver fibrosis. Liver biopsy is essential to confirm its diagnosis. The absence of specific clinical indicators in adults often leads to delays in diagnosis and management, while the natural history has not been well described. We sought to define the presentation and outcomes of adults with biopsy-proven CHF.

Materials and Methods: A retrospective chart review was conducted of patients diagnosed with CHF by liver biopsy. Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage of patients.

Results: We identified 24 patients evaluated over a 20-year period, with a median age of 51 years (range 22–72 years) at initial presentation; 14 were male. The most common imaging findings were renal cysts (91.3%), splenomegaly (69.6%), and a cirrhotic-appearing liver (60.9%). The most commonly treated liver-related complications were cholangitis (45.8%), varices (45.8%), and hepatic encephalopathy (25%). Two patients died with a median length of follow-up of 2.9 years (range: 0.0–20.0 years). Two patients underwent transjugular intrahepatic portosystemic shunt (TIPS) placement to manage bleeding esophageal varices. Eight patients underwent liver transplantation (LT), the most common indication being decompensated disease (50%).

Conclusions: CHF should be considered when patients present with cholangitis and/or complications of portal hypertension and have a cirrhotic appearing liver and renal cysts on imaging. Depending upon the disease severity, interventions such as TIPS or LT may be required.

1. Introduction

There are a variety of uncommon liver disorders whose natural history is variable, one being congenital hepatic fibrosis (CHF), a rare fibropolycystic disease in which patients have biliary tract changes and hepatic fibrosis [1]. This condition affects only one in 10,000-20,000 [2]. Complications typically include cholangitis and those related to portal hypertension (PHT), which can manifest as hepatic encephalopathy, bleeding varices, and ascites. These presentations are often more severe in children, prompting accelerated investigation and diagnosis. Adults, on the other hand, usually present more insidiously with abnormal liver function tests or abnormal imaging being the first indication. In patients with severe complications of CHF, measures including placement of a transjugular intrahepatic portosystemic shunt (TIPS) or even evaluation for liver transplant (LT) may be required. Liver biopsy is the gold-standard to diagnose CHF; however, signs of CHF may be appreciated on various imaging modalities and help expedite diagnosis and intervention. The pathophysiology of CHF is similar to that of other more common diseases such as polycystic kidney disease (PKD). Normal development of

Abbreviations: ALT, Alanine Aminotransferase; ARPKD, Autosomal Recessive Polycystic Kidney Disease; AST, Aspartate Aminotransferase; CHF, Congenital Hepatic Fibrosis; EV, Esophageal Varices; GFR, glomerular filtration rate; HCC, Hepatocellular carcinoma; HE, Hepatic Encephalopathy; INR, International Normalized Ratio; LT, Liver Transplant; MELD, Model for End-stage Liver Disease; MR, Magnetic Resonance; MRE, Magnetic Resonance Enterography; PKD, Polycystic Kidney Disease; PHT, Portal Hypertension; SLK, Simultaneous Liver and Kidney transplantation; TIPS, Transjugular Intrahepatic Portosystemic Shunt; US, Ultrasound

* Corresponding author.
E-mail address: Keaveny.andrew@mayo.edu (A.P. Keaveny).

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both the portobiliary system and renal tubules is contingent on *PKD* genes encoding proteins that migrate to the primary cilia. This may explain the association between autosomal recessive polycystic kidney disease (ARPKD) and CHF. In CHF specifically, cholangiocytes with defective cilia prevent appropriate development of the biliary system resulting in ductal plate malformation that presents as defects in the microscopic bile ducts [3]. Another presentation of ductal plate malformation is Caroli's disease, where larger intrahepatic bile ducts are inappropriately dilated [4]. Caroli's disease is also commonly found in patients with ARPKD.

Over the past two decades, significant advances in the non-invasive assessment of patients with liver disease utilizing detailed cross-sectional imaging (computerized tomography [CT] and magnetic resonance [MR] modalities) combined with elastography assessed by ultrasound (US) and MR techniques have revolutionized the approach to patients with liver disease. Strategies to evaluate and treat complications of PHT have evolved in concert with these imaging technologies. While management of cirrhosis appropriately dominates the literature, it is important to consider other chronic liver diseases such as CHF in the differential diagnosis, appreciate their natural history, and recognize their presentation and imaging findings as well as be familiar with the appropriate management. In this study, we sought to review our center's experience in managing adult patients (patients aged 18 or older at presentation) that were confirmed to have CHF on biopsy.

2. Material and Methods

We conducted a retrospective search of patients aged 18 or older with the diagnosis of CHF in our surgical pathology files from 2000 to 2020. Institutional Review Board approval was obtained for this minimal risk study (study number 21-013168, approved January 20th, 2022). Consequently, consent was not required to be obtained from study participants.

Cases were confirmed by an experienced liver pathologist. Characteristic features of CHF included the presence of a geographic pattern of fibrosis with islands of hepatocytes. Bile ducts were usually evenly distributed within the fibrous tissue reminiscent of bile duct hamartomas. Bile duct cysts and bile plugs could also occur. There usually was no or minimal inflammatory infiltrate. Patients with other liver disease were excluded from the study. A chart review was conducted for the clinical presentation, laboratory and radiographic studies, associated pathology findings, treatment, and outcome.

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage of patients. Statistical analysis was performed using R Statistical Software.

3. Results

A total of 24 adult patients were identified by an experienced liver pathologist for inclusion in this study. The patients were diagnosed by tissue examination with classic features of CHF. Geographic areas of fibrosis were present with evenly spaced ductal structures reminiscent of bile duct hamartomas (Figure 1). Occasional, small cysts could be found in most cases with inspissated bile (bile plugs) (Figure 2). Focal rupture of cysts with necrosis and associated inflammation could also be seen. Patient characteristics are shown in Table 1. The median age at initial presentation was 51 years (range: 22 – 72 years) and 14 patients (58.3%) were male. Of note, two patients were also diagnosed with Caroli's disease.

Findings on imaging studies obtained during initial patient workup and throughout the clinical journey are summarized in Table 2. The most common findings being renal cysts (91.3%), splenomegaly (69.6%), and a cirrhotic-appearing liver (60.9%). GFR, glomerular filtration rate; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; INR, International Normalized Ratio.

Table 3 demonstrates the mean liver stiffness of 6 patients who underwent MR elastography (MRE); the mean liver stiffness was

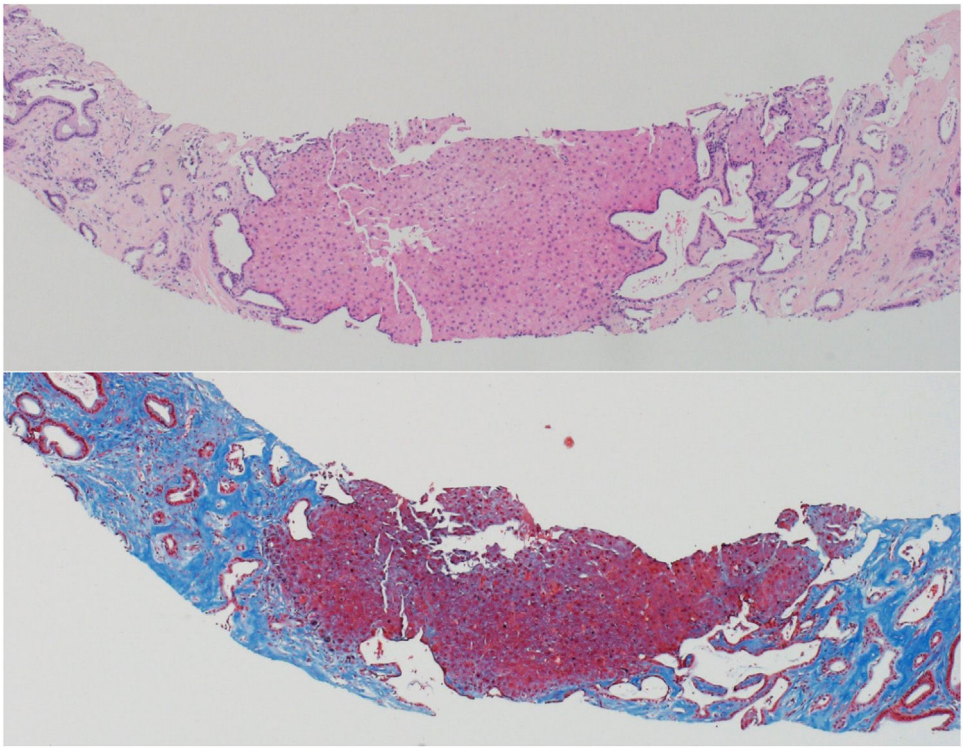

Fig. 1. Liver biopsy (H&E and trichrome stain) demonstrating characteristic features of CHF. Unevenly distributed bile ducts with irregular profiles. In the middle is an island of hepatic parenchyma.

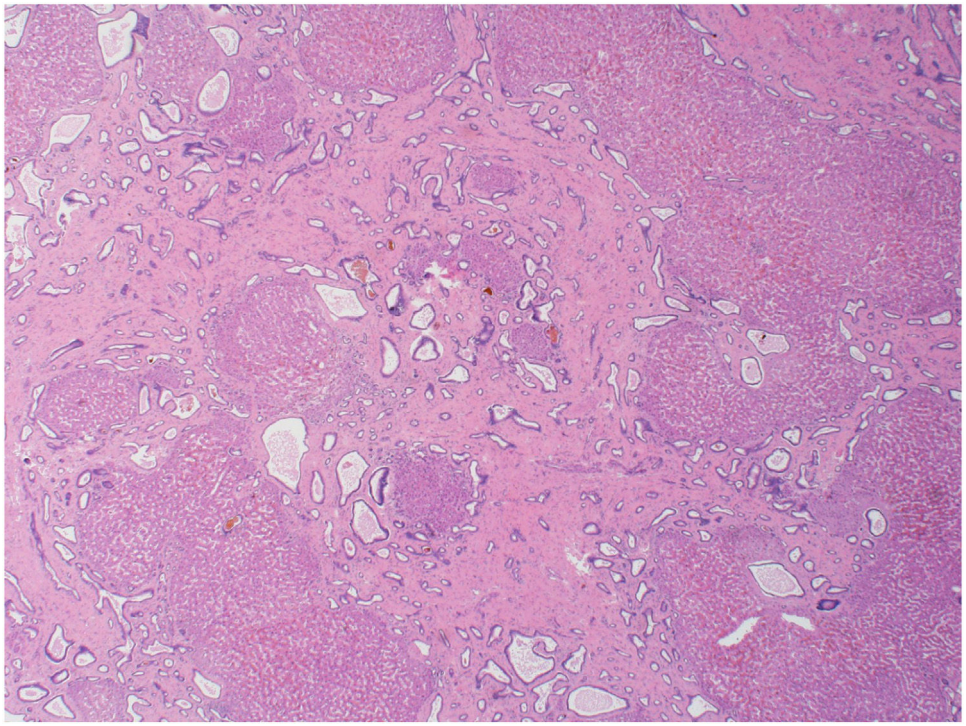

Fig. 2. Low power image of a liver with CHF. This image demonstrates geographic areas of fibrosis with evenly spaced bile ducts, some of which are dilated and contain bile plugs.

Table 1
Patient characteristics

Variable	N	Median (minimum, maximum) or Number (%) of patients
Age of initial presentation (years)	24	51 (22, 72)
Sex (male)	24	14 (58.3%)
Initial labs		
Estimated GFR	18	60.0 (12.4, 87.0)
Albumin (g/dL)	23	4.2 (1.9, 4.9)
Total bilirubin (mg/dL)	24	0.6 (0.2, 4.2)
Alkaline phosphatase (U/L)	22	111 (57, 1449)
AST (U/L)	22	39.5 (22.0, 151.0)
ALT (U/L)	22	35 (19, 203)
Total serum protein	17	6.8 (5.0, 8.3)
White blood cell count (Thousand/uL)	21	4.7 (2.1, 9.0)
Hemoglobin (g/dL)	20	12.9 (10.4, 14.3)
Platelet count (Thousand/uL)	21	135 (35, 484)
INR	23	1.1 (0.9, 1.6)
Creatinine	22	0.9 (0.6, 7.8)
Presence of Proteinuria	17	7 (41.2%)

2.8 kPa (range 2.3–7.4 kPa). Table 4 demonstrates the findings of 5 patients who were evaluated by transient elastography; the median liver stiffness was 10.8 kPa (range 1.6–33.8 kPa). Transhepatic portal venography pressure measurements were performed in two patients– the hepatic venous pressure gradients were 6 mmHg and 8 mmHg, respectively. Twenty patients had an endoscopy where esophageal and gastric varices were found in 9 (45%) and 1 (5%) patient, respectively. Six patients had small and 3 had medium sized esophageal varices (EV).

Complications associated with CHF and outcomes are shown in Table 5. The most common liver-related complications that required treatment were cholangitis (45.8%) and varices (45.8%). Of the 9 patients with EV, 8 patients experienced variceal bleedings that required treatment. Six patients (25%) were treated for hepatic encephalopathy and 5 patients (20.8%) developed ascites that necessitated treatment. Two patients required placement of a TIPS for management of recurrent EV bleeding. With a median length of follow-up of 2.9 years (range 0.0–20 years), two of the 24 patients (8%) died at 3.5 and 16.2 years after initial presentation while 8 patients underwent LT. The cumulative incidence death at five years following initial presentation was 9.1% (95% confidence interval: 0.0%–24.6%).

The indications for LT were decompensated chronic liver disease and recurrent cholangitis in 7 and 1 patient, respectively. Two patients underwent simultaneous liver and kidney transplant (SLK) – both had autosomal recessive polycystic kidney disease (ARPKD) and were prior renal transplant recipients. The mean biological model for end-stage liver disease (MELD) score at time of LT was 16 (range 8-25). Post-LT, one patient's recovery was complicated by the development of hepatic artery thrombosis, treated with emergent thrombectomy. They required retransplantation for complications of ischemic cholangiopathy 23 months later. Another patient required

Table 2
Summary of Imaging Findings

Imaging modality	Renal cyst(s)	Splenomegaly	Cirrhotic-appearing liver	Biliary tract changes	Presence of portosystemic collaterals	Varices	Arterial aneurysms	Ascites
MR (n = 18)	15 (83.3%)	11 (61.1%)	9 (50.0%)	9 (50%)	7 (38.9%)	6 (33.3%)	1 (5.6%)	0 (0%)
CT (n = 13)	8 (61.5%)	10 (76.9%)	5 (38.5%)	7 (53.8%)	5 (38.5%)	6 (46.2%)	2 (15.4%)	2 (15.4%)
US (n = 21)	11 (52.4%)	10 (47.6%)	8 (38.1%)	2 (9.5%)	3 (14.3%)	4 (19%)	0 (0%)	2 (9.5%)

Table 3
Mean Liver Stiffness of 6 Patients Who Underwent MR Elastography

Kilopascal (kPA)	2.3	2.5	2.6	2.9	3.6	7.4

Table 4
Summary of Transient Elastography Findings

Median liver stiffness (Kilopascal)	1.6	3.6	10.8	21.4	33.8
Median Shear Wave Speed (Meter/second)	0.72	1.11	N/A	2.67	3.36
Interquartile Range: Median Ration (Percentage)	6	13	21	10	7
Controlled Attenuated Parameter (decibels/minute)	174	185	309	325	312

Table 5
Liver- related complications and outcomes

Variable	N	Number (%) of patients
Liver-Related Complications Requiring Treatment	24	
Cholangitis		11 (45.8%)
Varices		11 (45.8%)
Bleeding Varices		8 (33.3%)
Hepatic encephalopathy		6 (25%)
Ascites		5 (20.8%)
Cholangiocarcinoma		1 (4.2%)
Hepatocellular carcinoma		1 (4.2%)
Death caused by complication	2	
Cholangiocarcinoma		1 (50%)
Hepatocellular carcinoma		1 (50%)

angioplasty of a hepatic artery anastomotic stenosis one-month post-transplant. Seven patients remain alive with a mean follow-up of 4.47 years (range 0.16–19.33). One patient died of metastatic hepatocellular carcinoma (HCC) that was diagnosed 11 months after retransplantation. The mean serum creatinine at last follow-up for the surviving patients was 1.1 mg/dL (range 0.6–8.4 mg/dL). No patient required renal replacement therapy or renal transplant.

4. Discussion

Congenital hepatic fibrosis is a rare disorder that has imaging similarities with cirrhosis and requires liver biopsy to confirm the diagnosis. This is the largest reported series from a single center describing the experience evaluating and managing adult patients with CHF. Perhaps due to its relative rarity, the diagnosis of CHF may have been delayed after clinical manifestations developed, given the average age at initial presentation to our medical center was 51 years. Fourteen patients (60.9%) were reported to have a cirrhotic-appearing liver on cross-sectional imaging. A notable finding of this study was that 91.3% of patients had renal cysts on imaging. Renal cysts across imaging modalities were typically multiple cysts of varying morphology, including simple to mildly complex with fluid or proteinaceous material. The presence of renal cysts may serve as an indication to consider performing a liver biopsy in patients with an abnormal appearing liver with or without stigmata of PHT.

The predominance of renal cysts in this population may be associated with *PKHD1*, the gene whose mutation is responsible for the development of ARPKD. *PKHD1* produces proteins that are structurally similar to hepatocyte-growth factor receptor [5]. This relationship may speak to the pervasive finding of renal cysts in our series. Gunay-Aygun and associates described the presentations and outcomes of 73 patients with ARPKD and CHF evaluated at the National Institutes of Health (NIH) [6]. In their cohort, 5 of the 17 adults had abnormalities in the renal medulla on ultrasound while 6 had abnormalities in both the renal cortex and medulla.

A minority of our patients underwent assessment by elastography using either US or MR-based techniques. While the data were limited, only 1 patient had a liver stiffness measurement consistent with stage 4 fibrosis. Therefore, in our opinion, discordance between elastography measurements and imaging findings should prompt consideration for proceeding with liver biopsy.

Biliary tract changes including ductal dilation and hamartomas were found in 47.8% of patients. This is to be expected, as abnormalities in the ductal plate resulting in biliary malformations seem to be a predominant mechanism in the pathogenesis of CHF [1]. Typically, in CHF, the ductal plate defect occurs at the level of the smaller interlobular bile ducts. This may explain why cholangitis was the most common liver-related complication that required treatment in our cohort. In the NIH series, 12 of the 17 adults with ARPKD and CHF had Caroli syndrome and three experienced cholangitis [5]. Portal hypertension resulting in the formation of varices was associated with significant morbidity, as 9 patients required treatment for bleeding EV. Malignancy can complicate CHF- 1 of our patients developed HCC and another patient developed cholangiocarcinoma. While surveillance for primary hepatic malignancy has not been recommended for patients with CHF [7], our experience suggests periodic imaging is appropriate.

Liver transplantation was required in nearly one-third of our patients due to the development of complications related to end-stage liver disease. Two patients required SLK, with their original underlying kidney disease being ARPKD. No adult patient in the NIH series underwent LT – our cohort was older with a mean age of 47 ± 25 years compared with 33.3 ± 11.3 years [6]. Outcomes post-LT were satisfactory. In a review of the US Scientific Registry of Transplant Recipients, 197 patients underwent LT for CHF between 2002 and 2018 [4]. A majority (75%) received LT alone, the remainder receiving SLK. Similar to our single center experience, the long-term graft and patient survival was excellent.

This report is limited by a lack of standardized follow-up and the evolving application of elastography over the last decade. However, our experience highlights the continuing role of liver biopsy in differentiating cirrhosis from conditions like CHF when there is discordance between elastography and liver imaging or extra-hepatic findings such as renal cyst(s). Cholangitis was the most common clinical complication of our cohort requiring management, followed by complications of PHT. Deterioration in liver function can occur in CHF and LT remains an appropriate treatment for patients manifesting with features of decompensated chronic liver disease. Primary liver malignancy may develop in patients with CHF, but like the disease itself, additional research is required to identify those at risk, the appropriate surveillance, and means to reduce the risk of morbidity and mortality associated with CHF.

5. Conclusions

Our study emphasizes the importance of considering CHF among adult patients with portal hypertension, cholangitis, and renal cysts without evident etiology. Although imaging studies alone are not sufficient to diagnose CHF, appreciation of fibropolycystic disease in the liver and other organs can provide the clinical context needed to advocate for liver biopsy.

Author contributions

L.L. contributed to analysis and interpretation of data and drafting and critical revision of the manuscript. J.L. contributed to acquisition of data. Z.P. and M.G.H. contributed to analysis and interpretation of

data. R.N. and A.P. K. contributed to study concept and design and critical revision of the manuscript.

Declaration of interests

None.

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