

Congenital hepatic fibrosis: clinical presentation, laboratory features and management at a tertiary care hospital of Lahore

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Abstract

Objective: To describe the clinical presentations, laboratory features and management of congenital hepatic fibrosis patients at a tertiary care hospital.

Methods: The case series was conducted at The Children Hospital and Institute of Child Health, Lahore, Pakistan, from July 2013 to June 2015, and comprised patients of congenital hepatic fibrosis diagnosed on the basis of liver biopsy. SPSS 20 was used for statistical analysis.

Results: The mean age of 25 patients in the study was 8.5 ± 2.74 years, and the male-to-female ratio was 3:1. Parents of 21(84%) patients had consanguineous marriage, and 14(56%) patients had family history of hematemesis and melena. Besides, 15(60%) patients presented with hematemesis, 12(48%) had abdominal distension, 5(20%) were picked up on screening of siblings and 5(20%) were referred from general practitioners on feeling of hepatosplenomegaly during routine examination. All had hepatomegaly with a mean size of 7.2 ± 2.3 cm palpable in midline. Splenomegaly was present in 24(96%). Overall, 15(60%) patients had oesophageal varices. Endoscopic band ligations were done in oesophageal variceal patients who were successfully managed, while 5(20%) patients required portosystemic shunt surgeries.

Conclusion: Congenital hepatic fibrosis was not uncommon in our population having high rate of consanguinity and most of them were familial cases.

Keywords: Congenital hepatic fibrosis, Hepatomegaly, Hematemesis. (JPMA 66: 984; 2016)

Introduction

Congenital hepatic fibrosis (CHF) is an autosomal recessive disorder. This is a developmental disorder of the portobiliary system and is characterised pathologically by defective remodelling of the ductal plate. Ductal plate is the embryological precursor of the biliary system and its malformations causes abnormal branching of the intrahepatic portal veins and progressive fibrosis of the portal tracts.¹ In 1856, the liver-related clinical presentations were first described² and in 1961, Kerr described different clinical manifestations of CHF.³ It belongs to the disorders grouped as fibropolycystic diseases (having abnormally high degree of fibrosis and presence of cysts in liver and kidneys) which include Caroli disease, autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD). These disorders are grouped together, but these are not a single entity, and represent a broad spectrum of hepatic and renal lesions.⁴ Clinically, there is presence of firm or hard hepatomegaly nearly in all patients, often with palpable left lobe and splenomegaly in most of the patients. Hepatocellular functions are

relatively well-preserved and complications are portal hypertension (PH), gastro-oesophageal varices and hypersplenism.^{1,5} Data regarding exact incidence and prevalence of CHF is not known, but estimated prevalence is 1 in 10,000 to 20,000.^{1,5} In 1978, Kerr reported 30 cases of CHF and described their long-term outcome.⁶ Poddar U. et al. published 15 cases of CHF from India in 1999.⁷ Only a few hundred patients with CHF have been reported in literature.⁸⁻¹³ There is no published data regarding CHF in Pakistan. The disease can be sporadic and its familial patterns have also been reported. With the high rate of consanguineous marriages in our country, our population is prone to developing these autosomal recessive disorders. Some cases of CHF due to presence of firm hepatomegaly and splenomegaly are managed as chronic liver disease. There is need for awareness of this entity among healthcare professionals for proper diagnosis and timely referral to paediatric gastroenterologist and hepatologist. Liver biopsy is important to sort out proper diagnosis in our setup where genetic mutation analysis facility is lacking. Moreover, if children with CHF are to be successfully treated for oesophageal varices, awareness regarding early diagnosis of this disease is required.

The current study was planned to describe the clinical presentations, laboratory features and management of CHF patients at a tertiary care hospital.

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Patients and Methods

The case series was conducted at the Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children Hospital and Institute of Child Health, Lahore, Pakistan, from July 2013 to June 2015. After approval from the institutional ethics review committee, patients were selected from among those who presented with hepatomegaly, splenomegaly and had no jaundice before undergoing liver biopsy. All patients diagnosed as CHF on liver biopsy were included in the study. Main confirmatory test for diagnosis in our setup is liver biopsy which shows bands of fibrous tissues often containing linear or circular spaces lined by cuboidal epithelium. Presence of diffuse portal and perilobular fibrosis which vary in thickness and intact lobular structures are main features. The limiting plate is intact and parenchyma is separated by islands of fibrosis. There are no inflammatory changes and regenerative nodules are absent. Biopsy findings exclude liver cirrhosis and other liver parenchymal diseases.

In our study, patients of Caroli syndrome were excluded because they were diagnosed on the basis of computed tomography (CT) scan of the abdomen and liver biopsies were not performed due to dilated biliary ducts.

A detailed patient history, including age on admission, gender, consanguinity, family history, presenting symptoms like hematemesis and melena, and physical examination, especially of the abdomen, were noted. Haematology, coagulation profile and liver function test (LFT) were

studied. Ultrasound of abdomen for liver and kidneys was done. Oesophagogastroduodenoscopy (EGD) was done in all patients and presence of oesophageal varices was determined at admission and findings were recorded.

SPSS 20 was used for statistical analysis. Frequency and percentage were computed for different numerical and categorical variables like age, gender, clinical features and complications.

Results

The mean age of 25 patients in the study was 8.5 ± 2.74 years (range: 2-14 years). There were 19(76%) boys and 6(24%) girls, with a male-to-female ratio of 3:1. Parents of 21(84%) patients had consanguineous marriage, and 14(56%) patients had family history. There were six families having more than one child with CHF, out of which 2(33.3%) families had history of deaths of children with severe hematemesis. Two (33.3%) families also had history of deaths in first cousins with hematemesis.

In terms of presentation, 15(60%) patients presented with hematemesis, 12(48%) had abdominal distension, 5(20%) were picked on screening of siblings and 5(20%) patients were referred from general practitioners on suspicion of hepatosplenomegaly on routine examination. All had hepatomegaly with a mean size of 7.2 ± 2.3 cm (range: 3-11cm) palpable in midline. Splenomegaly was present in 24(96%) with palpable spleen mean 5.2 ± 1.51 cm (range: 3-9cm). One (4%) patient who was picked up on screening

Table: Complete blood counts and Liver function tests of CHF patients.

	Mean	Std. Deviation ($\pm$)	Minimum	Maximum
Haemoglobin (gm/dl)	10.3737	1.31184	8.50	12.50
WBC (109/l)	6.0521	3.88661	1.85	12.30
Platelets (109/l)	177.0526	104.65206	65.00	345.00
Serum Bilirubin (mg/dl)	0.5011	0.16367	0.30	0.90
ALT (IU/l)	26.5789	5.65013	14.00	41.00
AST (IU/l)	27.9474	4.70784	19.00	35.00
ALP (IU/l)	230.4211	75.17780	145.00	492.00
GGT (IU/l)	63.28	23.7162	32	121
Albumin (gm/dl)	4.7474	0.38205	4.00	5.30
PT (seconds)	10.5789	0.37055	10.00	11.20
INR	1.0616	0.03891	1.00	1.15
APTT (seconds)	26.0000	2.10819	22.00	29.00

CHF: Congenital hepatic fibrosis

WBC: White blood cell

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

ALP: Alkaline phosphatase

GGT: Gamma-glutamyl transpeptidase

PT: Prothrombin time

INR: International normalised ratio

APTT: Activated partial thromboplastin time.

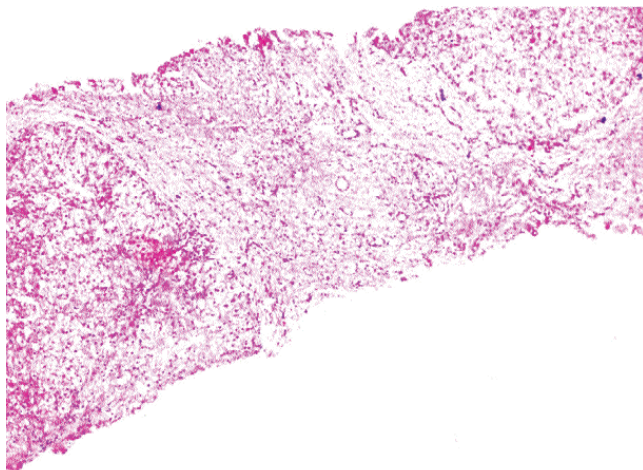


Figure-1: Panoramic view illustrating a section of liver biopsy composed of portal tracts and hepatocytes. The portal tract has broad fibrous expansion with intervening bile ducts and adjacent hepatocytes are unremarkable.

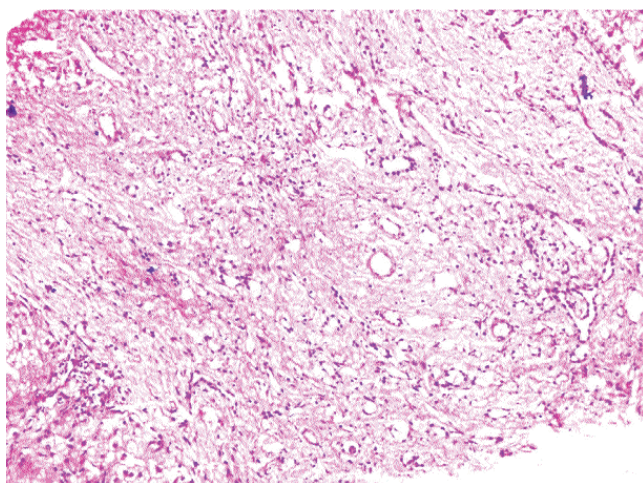


Figure-2: A high-power view reveals enlarged portal tracts owing to the irregular deposition of collagen. No inflammation is evident in this view and adjacent hepatocytes are unremarkable.

had no splenomegaly. Two (8%) patients had associated portal vein thrombosis. Two (8%) children had associated renal cysts and slightly dilated biliary channels were noted at the peripheral parts of both lobes of liver. Two (8%) children were associated with medullary sponge kidney and 1 (4%) patient was found to have absent right kidney and compensatory hypertrophied left kidney. All the 5(20%) had normal renal functions. Moreover, 15(60%) patients had oesophageal varices; 9(36%) Grade IV varices; 4(16%) Grade III; and 2(8%) Grade II. In 10(40%) patients, surveillance endoscopy showed no oesophageal varices.

Laboratory results showed mean haemoglobin

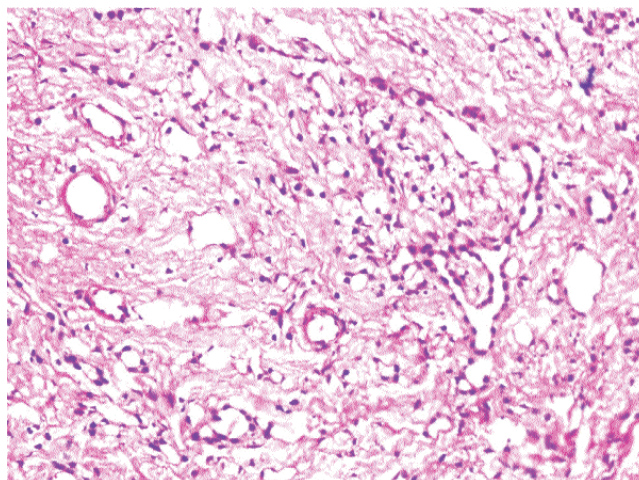


Figure-3: A high-power view reveals abnormally shaped bile ducts in the fibrous tissue along the septal margin. No bile plugs are evident and adjacent hepatocytes are unremarkable.

10.3±1.3gm/dl, total leukocyte count (TLC) 6.0±3.8* 10⁹/l, platelets 177±104.6* 10⁹/l, serum bilirubin 0.5±0.1mg/dl, serum alanine aminotransferase (ALT) 26±5.6IU, serum aspartate aminotransferase (AST) 28±4.7IU, serum alkaline phosphatase (ALP) 230±75.1IU, serum gamma-glutamyl transpeptidase (GGT) 63.28±23.7IU, serum albumin 4.75±0.3gm/dl, prothrombin time (PT) 10.5±0.3 seconds, international normalised ratio (INR) 1.06±0.03 and activated partial thromboplastin time (APTT) 26±2.1 seconds (Table). Overall, 14(56%) patients had hypersplenism. Endoscopic band ligations (EBL) were done in oesophageal variceal patients and were successfully managed for varices, while 5(20%) patients required portosystemic shunt surgeries. One (4%) of the older child who underwent shunt surgery developed renal failure on follow-up. Total 6(24%) patients had renal involvement during the study period and deranged renal function test was found in only 1(4%) patient.

Tissue histopathology images of liver biopsy of CHF patients are shown in Figure 1, 2 & 3.

Discussion

Congenital hepatic fibrosis is a one of the subtype of spectrum of fibropolycystic diseases (FCDs) with a variable clinical presentation which depends upon the time of presentation and degree of hepatic and renal involvement.

In our study, the mean age of presentation was 8.5 years with range of 2-14 years. One study also described the same age range in a review of 51 patients (1.8-14 years).¹⁴ In our study, consanguinity was present in majority of cases and six families had more than one child affected. There was high prevalence of CHF in inbred community in our study.

Portal hypertension (PH) and bleeding oesophageal varices

is the most common clinical presentation or complication of CHF. In our study, 60% patients presented with hematemesis, majority were from older age group of patients. Patients picked up with organomegaly and screening had no developed varices. It is a progressive process, and with the passage of time hepatic fibrosis increases and PH worsens. There is increase in splenic size, decrease in platelets and white blood cells (WBCs) (hypersplenism), and there is development of porto-systemic vascular collaterals, including oesophageal and gastric varices. Rawat D. et al. described PH and oesophageal varices in 86% patients.¹⁵ Srinath & Shneider from major review of CHF patients also described the presence of PH in a high percentage of individuals with isolated CHF (iCHF), which is the most common mode of clinical presentation of iCHF.¹⁶

Hepatomegaly with predominant involvement of the left lobe is present in nearly all patients and in most patients splenomegaly is associated with evidence of hypersplenism. Anaemia, thrombocytopenia and leukopenia develop in CHF usually after the development of hypersplenism, secondary to PH. In our study more than half of the patients had hypersplenism and had documented decrease in number of platelets and white cell counts. We found normal liver enzymes and synthetic functions in all patients. Liver enzyme levels are usually within the reference range except in cholangitis form of CHF in which repeated episodes of cholangitis can lead to raised liver enzymes and decline in synthetic liver function.¹⁰ Normal liver function does not correlate with the severity of PH and sometime we can have deranged liver enzymes, ascites and prolonged PT during severe active bleed.

The main confirmatory test for diagnosis in our setup is liver biopsy which shows bands of fibrous tissues often containing linear or circular spaces lined by cuboidal epithelium. Presence of diffuse portal and perlobular fibrosis which vary in thickness and intact lobular structures are main features. The limiting plate is intact and parenchyma is separated by islands of fibrosis. There are no inflammatory changes and regenerative nodules are absent.¹⁴ Liver biopsy is also important to differentiate from other autosomal recessive condition, Wilsons disease, which can also present with normal liver enzyme and hepatomegaly.¹⁷ That condition is commonly present in our population owing to high rates of cousin marriages.

It is reported in literature that many other conditions can be associated with CHF. These hepatorenal FCDs can be inherited as a multisystem disorder in an autosomal recessive, autosomal dominant, or X-linked recessive manner. Clinical presentation of these hepatorenal FCDs suggest the diagnosis, but sometime diagnostic approach may be difficult

because there is significant overlap in phenotype and the genes associated. These include Meckel syndrome (MKS, which is associated with pathogenic variants in 11 genes: MKS1, TMEM216, CEP290, RPGRIP1L, CC2D2A, NPHP3, TCTN2, B9D, B9D21 & TMEM231), Nephronophthisis (NPHP in 15 genes: NPHP1, INVS, NPHP3, NPHP4, IQCB1, CEP290, GLIS2, RPGRIP1L, NEK8, TMEM67, TTC21B, WDR19, ZNF423, CEP164 & ANKS6), Joubert syndrome and related disorders (JSRDs in 20 genes: INPP5E, TMEM216, AHI1, NPHP1, CEP290, TMEM67, RPGRIP1L, ARL13B, CC2D2A, OFD1, TTC21B, KIF7, TCTN1, TMEM237, CEP41, TMEM138, C5orf42, TCTN3, ZNF423 & TMEM231), Bardet-Biedl syndrome (BBS in 14 genes: BBS1, BBS2, ARL6, BBS4, BBS5, MKKS, BBS7, TTC8, BBS9, BBS10, TRIM32, BBS12, MKS1 & CEP290), Cranioectodermal dysplasia (CED: IFT122 gene), Ellis-van Creveld syndrome (EVC: EVC gene), Jeune asphyxiating thoracic dystrophy (JATD: JATD 1 & 2 gene), Renal-hepatic-pancreatic dysplasia (RHPD: NPHP3 gene) and Oral-facial-digital syndrome type 1 (OFD1 gene).¹ These conditions were not seen in our cohort of patients. Renal involvement was present in 5 patients at diagnosis: two had associated renal cysts, two had medullary sponge kidney and one patient was found to have absent right kidney and compensatory hypertrophied left kidney. Our sixth patient developed renal failure during follow-up visits. Total one-fourth patients had renal involvement and the remaining three-fourth patients had iCHF. We have kept all these patients in follow-up for possible renal involvement in future. Gunay-Aygun M. et al. described 73 patients having CHF and ARPKD (confirmed by detection of mutations in PKHD1), including adult patients. In 26% patients, initial symptoms were liver-related and they documented the independent nature of renal and hepatic involvement in ARPKD.¹⁸

Isolated CHF has also been documented and defined in literature. The responsible gene(s) having mutation for iCHF are unknown. Srinath & Shneider in review article described that majority (64%) of the cases were classified as ARPKD/CHF and 9.5% were diagnosed as iCHF.¹⁶

The cholangitis form of CHF is also defined in the literature and differentiation from Caroli's disease is difficult. The bile ducts involved in Caroli's disease are bigger and segmental. But in CHF, the smaller and peripheral bile ducts are involved.¹⁹ We had two patients diagnosed as Caroli's syndrome on the basis of CT scan and both were excluded from the study as we included only biopsy-proven patients of CHF. In the included patients, two had slight bile duct dilatations in peripheral parts of lobes of liver. Although pathologically, an overlap between Caroli's disease and CHF has been found and simultaneous presence of Caroli's disease, CHF and polycystic kidneys is labelled as Caroli's syndrome.

CHF cannot be completely cured. There are no such

therapies that can correct the underlying defect, stop progression or reverse the degree of fibrosis and normalise the abnormalities of biliary tree. Complications of CHF are variceal bleeding, hypersplenism, cholangitis and, to a lesser extent, biliary stones and cholangiocarcinoma mainly reported in adult patients.¹⁶ Early recognition and proper management of complications can decrease mortality and morbidity in CHF patients.

In our study, major complication was portal hypertension in majority of patients. Patients with acute bleeding episode were medically managed with octreotide, fluids and blood products followed by elective or emergency endoscopic Sclerotherapy or band ligation. Oral medicine (propranolol as prophylaxis) was given to patients having oesophageal varices. Our five patients who had repeated variceal bleeding underwent shunt surgery. Shneider BL. et al. also described standard paediatric-specific surveillance and similar management approaches to these problems in children.²⁰

CHF is a distinct entity from many other chronic liver diseases of childhood in that these patients are not typically prone to developing progressive hepatic insufficiency.¹⁶ Most patients do well and the prognosis of CHF is dependent on management of bleeding secondary to portal hypertension and it may be greatly improved by shunt surgery, but survival in some patients is dependent on the degree of renal involvement and renal failure.³

Conclusion

CHF is not uncommon in our population having high rate of consanguinity and most of them were familial cases. Most common presentation was hematemesis and hepatosplenomegaly, with hepatomegaly mainly of left lobe. Liver enzymes and synthetic functions were normal. One-fourth patients had renal involvement. EBL is effective way for management of oesophageal varices followed by shunt surgery in refractory cases. If bleeding from varices can be controlled and there is no renal involvement, the prognosis of congenital hepatic fibrosis is favourable.

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Conflict of Interest: No.

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