



Hepatorenal Fibrocystic Diseases: disease spectrum, clinical presentations and complications

Thesis

**Submitted for fulfillment for
Master Degree in Pediatrics**

Presented by

Rehab El Sayed Mohamed Abd El Salam

Under supervision of

Prof. Dr. Rokaya Mohamed El Sayed Mohsen

Professor of pediatrics

Faculty of Medicine – Cairo University

Prof. Dr. Mona El Said El Raziky

Professor of pediatrics

Faculty of Medicine – Cairo University

Prof. Dr. Rascha Essam El Din Abd El Aziz

Lecturer of Pediatrics

Faculty of Medicine – Cairo University

Cairo University

2013

Abstract

In this case series descriptive study, we aimed at describing the clinical presentations and complications of congenital hepatic fibrosis. The study was conducted on patients attending the hepatology clinic Cairo University Pediatric Hospital (CUPH) from November 2011 to June 2013. **Methods:** Patient's data were retrieved from patient's files. Twenty nine patients with age range from 0.6 to 13.2 years were included; they were 19 males and 10 females. History of the presenting illness, clinical examination, and laboratory investigations were recorded. Ultrasound and upper endoscopic findings as well as liver biopsy findings were recorded as well. Diagnosis of congenital hepatic fibrosis depends on clinical, ultrasonographic findings as well as liver biopsy. **Results:** The main presenting symptoms were abdominal distension in 15 patients (51.7%), followed by hematemesis in 11 patients (37.9%). Failure to thrive was detected in the form of weight below 3rd percentile in 10 patients (38.5%). Hepatomegaly was the main clinical finding in the studied patients as it was detected in 24 patients (82.8%). Evidence of portal hypertension, manifested by splenomegaly was detected in 21 patients (72.4%) and esophageal varices in 20 patients (69%) of patients. Recurrent cholangitis presenting with fever, jaundice in an already diagnosed CHF patients was detected in 3 patients (10.3%). Intra-hepatic biliary radical's dilatation was found by ultrasound examination in 5 patients (17.2%). Increased kidney size was detected in 10 cases (34.5%), renal calcification was detected also in 10 cases (34.5%), renal cysts in 9 cases (31%), hyperechogenic kidney in 4 patients (13.8%), loss of cortico-medullary differentiation in 4 cases (13.8%), and renal stone was found in one case (3.4%). Unfortunately one of the studied patients died of hematemesis complicating esophageal varices. **Conclusion:** Portal hypertension was the main clinical presentation of congenital hepatic fibrosis. Renal involvement,

the other spectrum of fibrocystic hepatorenal disease, is somewhat common in our cases.

Key words:

Congenital hepatic fibrosis, children, Hepatorenal fibrocystic diseases, portal hypertension.

First and foremost thanks to

Allah

The beneficent and merciful of all

Acknowledgment

I wish to express my deepest gratitude and sincerest thanks to Prof. Dr. Rokaya Mohamed El Sayed Mohsen, professor of pediatrics, faculty of medicine – Cairo University, for her kind continuous supervision, valuable guidance and encouragement at every step of the work.

I am also deeply indebted and extremely grateful to Prof. Dr. Mona El Said El Raziky, professor of pediatrics, faculty of medicine – Cairo University, for her supervision, valuable guidance and faithful help.

I am also deeply grateful indebted to Dr. Rascha Essam El Din Abd El Aziz, lecturer of pediatrics, faculty of medicine – Cairo University, for her supervision and offering every possible help.

I would like to thank my family for their continuous help and support.

Contents

	Item	Page
1	Introduction	1
2	Aim of work	3
3	Review of literature	4
	• Hepatorenal fibrocystic diseases	5
	• Genotype-phenotype correlation	12
	• Phenotypic features shared by the hepatorenal FCDs	13
	• Definition of CHF	15
	• Pathophysiology of CHF	16
	• Pathology	18
	• Epidemiology	21
	• Clinical manifestation of CHF	22
	• Mortality and morbidity	26
	• Differential diagnosis	27
	• Diagnosis	30
	• Evaluation strategy	37
	• Management	41
4	Patients and methods	48
5	Results	53
6	Discussion	80
7	Conclusion and recommendations	89
8	References	91
9	Summary	111
10	Arabic summary	

List of abbreviations:

ADPKD	Autosomal dominant polycystic kidney disease
ALP	Alkaline phosphatase
ALT	Alanine transferase
ANA	Anti nuclear antibody
ARPKD	Autosomal recessive polycystic kidney disease
ASMA	Anti smooth muscle antibodies
AST	Aspartate transferase
BBS	Bardet-Biedl syndrome
CD	Caroli disease
CDC	Centers for disease control
CDG-Ib	Congenital disorder of glycosylation type 1b
CED	Cranioectodermal dysplasia
CHF	Congenital hepatic fibrosis
CS	Caroli syndrome
CT	Computed tomography
CUPH	Cairo University Pediatric Hospital
DHPLC	Denaturing high performance liquid chromatography
DPM	Ductal plate malformation
EGD	Esophago-gastro-duodenoscopy
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease
EVC	Ellis-Van Creveld syndrome
FCDs	Fibrocystic diseases
GGT	Gamma glutamyl transferase
HRFCDs	Hepatorenal fibrocystic diseases
IQ	Intelligence quotient
JATD	Juvenile asphyxiating thoracic dystrophy
JSRDs	Joubert syndrome and related disorders
MHz	Mega Hertz
MKS	Meckel syndrome
MRCP	Magnetic resonant cholangiopancreatography
MRI	Magnetic resonant
MTS	Molar tooth sign
NIH	National Institutes of Health
NPHP	Nephronophthisis
NSAIDs	Non steroidal anti-inflammatory drugs
OFD1	Oral-facial-digital syndrome type 1
PANCA	Perinuclear Anti-Neutrophil cytoplasmic antibodies
PBC	Primary biliary cirrhosis

PFIC	Progressive familial intrahepatic cholestasis
PH	Portal hypertension
PKHD1	Polycystic kidney and hepatic disease 1
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
RHPD	Renal-hepatic-pancreatic dysplasia
TIPS	Transjugular intrahepatic portosystemic shunts
VMC	Von meyenburg complex
VOD	Veno-occlusive disease

List of figures of review:

Figure N.	Figure name	Page N.
Figure 1	Brain MRI in BBS and joubert syndrome patients	8
Figure 2	Oral and digital abnormalities in OFD1	11
Figure 3	Ductal plate malformation	17
Figure 4	Dilated bile ducts in caroli syndrome	19
Figure 5	Macrocyts in ARPKD	20
Figure 6	Biliary hamartomas	29
Figure 7	Renal ultrasonography showing enlarged cystic left and right kidney	32
Figure 8	MRI of intrahepatic bile ducts in CHF	33
Figure 9	Medullary sponge kidney by MRCP	34
Figure 10	Portal fibrosis with dilated biliary channels	36

List of figures of results:

Figure N.	Figure name	Page N.
Figure 11	Sex distribution of the study group	55
Figure 12	Complaint of the study group	56
Figure 13	History of the study group	58
Figure 14	Weight percentiles of the study group	59
Figure 15	Height percentiles of the study group	60
Figure 16	Examination of the study group	61
Figure 17	Abnormal laboratory tests	65
Figure 18	Ultrasound findings of liver, gall bladder and spleen	68
Figure 19	Renal ultrasound findings	70
Figure 20	Liver histology	72
Figure 21	Type of presentation	73
Figure 22	Complications in the study group	77
Figure 23	Medications used in the study group	79

List of tables of methodology:

Table N.	Table name	Page N.
Table I	Normal hemoglobin values according to age	50
Table II	Normal white blood cells values according to age	51

List of tables of results:

Table N.	Table name	Page N.
Table 1	Sex distribution of the study group	54
Table 2	Complaint of the study group	56
Table 3	History of the study group	57
Table 4	Weight percentiles of the study group	59
Table 5	Length/height percentiles of the study group	60
Table 6	The positive findings on the examination	61
Table 7	The liver size in MCL and midline	62
Table 8	CBC components of the studied patients	63
Table 9	Laboratory results of the studied patients	64
Table 10	Abnormal laboratory tests	66
Table 11	Ultrasound findings of liver, gall bladder and spleen	67
Table 12	Renal ultrasound findings	69
Table 13	Comparison of clinical findings between patients presented below and above 5 years	71
Table 14	Histopathological examination of the liver	72
Table 15	Type of presentation of CHF in the study group	73
Table 16	Comparison of liver histology findings between patients with and without IHBRD on liver histopathological examination	74
Table 17	Comparison of some data between patients with and without IHBRD on ultrasound	75
Table 18	Complications in the study group	76
Table 19	Medications used in the study group	78

Introduction
And aim of the work

Introduction:

Congenital hepatic fibrosis (CHF) is a histopathologic diagnosis that refers to a developmental disorder of the portobiliary system characterized by ductal plate malformation (DPM), abnormal branching of the intrahepatic portal vein, and progressive fibrosis of the portal tracts.

Ductal plate malformation results in a range of abnormalities depending on the level of the biliary tree primarily involved:

- CHF without macroscopically visible cystic dilatation of the intrahepatic biliary ducts.

- CHF associated with macroscopic liver cysts in continuity with the bile ducts, sometimes referred to as Caroli's syndrome (CS) (*Desmet, 1998*).

Most frequently CHF\CS is associated with ciliopathies (disorders of the primary cilia) that have associated renal disease: polycystic kidney disease, nephronophthisis (NPHP), and chronic tubulointerstitial disease, collectively referred to as the hepatorenal fibrocystic diseases (HRFCDs) (*Summerfield et al., 1986*).

The characteristic clinical picture of the CHF is portal hypertension (PH) which is strictly defined as an increase in the portal venous pressure (*Kerr et al., 1978 & Summerfield et al., 1986*).

In general, as hepatic fibrosis increases and PH worsens, the spleen increase in size, platelets and white blood cells decrease in number (hypersplenism) and porto-systemic vascular collaterals develop, including esophageal and gastric varices. As varices enlarge, the risk of bleeding increases (*Kerr et al., 1978; Summerfield et al., 1986; Fonck et al., 2001*).

Pulmonary hypertention (portopulmonary hypertention) and vascular shunts in the pulmonary parenchyma (Hepatopulmonary syndrome) are complications of PH that can also be rarely seen in CHF (*Kerr et al., 1978; Summerfield et al., 1986; Fonck et al., 2001*).

Cholangitis should be considered and investigated in individual known to have biliary dilatation that develop unexplained fever or right upper-quadrant pain with or without jaundice (*Shneider & Magid, 2005*).

Ultrasound examination is the most informative diagnostic modality in CHF which often reveals: increased echogenicity of the liver, cysts in the hepatic parenchyma, enlarged spleen and accompanying fibrocystic changes in the kidneys (*Premkumer et al., 1988 & Akhan et al., 2007*).

Histopathologic finding on liver biopsy are the gold standard for diagnosis of CHF (*Fonck et al., 2001*).

There is no known treatment for the underlying defect in CHF because no therapies can repair the primary ductal plate malformation or reverse the fibrosis or biliary tree abnormalities (*Shneider & Magid, 2005*).

Aim of the work:

To describe the clinical presentation and complications of CHF patients presenting and following up in the hepatology unit of Cairo University Pediatric Hospital (CUPH).

Review of literature