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Congenital Hepatic Fibrosis Overview — RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

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Clinical characteristics

Congenital hepatic fibrosis (CHF) is a developmental disorder of the portobiliary system characterized histologically by defective remodeling of the ductal plate (ductal plate malformation; DPM), abnormal branching of the intrahepatic portal veins, and progressive fibrosis of the portal tracts. CHF may or may not be associated with macroscopic cystic dilatation of the intrahepatic bile ducts. Clinical findings include enlarged, abnormally shaped liver, relatively well-preserved hepatocellular function, and portal hypertension (PH) resulting in splenomegaly, hypersplenism, and gastroesophageal varices. Pulmonary hypertension (portopulmonary hypertension) and vascular shunts in the pulmonary parenchyma (hepatopulmonary syndrome), complications of PH, can also be seen rarely. Most frequently CHF is associated with ciliopathies (disorders of the primary cilia) that have associated renal disease, the so-called hepatorenal fibrocystic diseases (FCDs). Although the hepatorenal FCDs are currently classified by phenotype, it is likely that gene-based classification will be quite different in the future because of the tremendous genetic and phenotypic overlap between these disorders.

Diagnosis/testing

CHF is typically diagnosed by finding increased echogenicity of the liver parenchyma with or without macrocysts on ultrasound examination; MRI including magnetic resonance cholangiopancreatography (MRCP)

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may also be used. Liver biopsy is rarely required. The multisystem syndromes associated with hepatorenal FCDs are diagnosed by physical examination or other specialized studies, family history, and molecular genetic testing.

Genetic counseling

The syndromes associated with CHF are most commonly inherited in an autosomal recessive manner; however, X-linked and autosomal dominant inheritance are also observed. Genetic counseling depends on accurate determination of the specific genetic diagnosis.

Management

Treatment of manifestations: No therapies can repair the primary ductal plate malformation or reverse the fibrosis or biliary tree abnormalities. Complications of CHF, including variceal bleeding, hypersplenism, cholangitis, and, to a lesser extent, biliary stones, cholangiocarcinoma, and hepatocellular carcinoma, are treated in a routine manner.

Prevention of secondary complications: Immunization for hepatitis A and B.

Surveillance: Monitor growth rate in children; screen for gastroesophageal varices and hepatopulmonary syndrome when the platelet count decreases significantly over time or prior to interventions such as renal transplantation.

Agents/circumstances to avoid: Alcohol, obesity, diabetes mellitus, malnutrition, infection with human immunodeficiency virus (HIV), immunosuppression, hepatotoxic medicines, nonsteroidal anti-inflammatory drugs (NSAIDs) in those with varices because of the increased risk of bleeding, contact sports/activities in those with splenomegaly because of the increased risk of splenic injury.

Definition

Clinical Manifestations of Congenital Hepatic Fibrosis

Congenital hepatic fibrosis (CHF) is a histopathologic diagnosis that refers to a developmental disorder of the portobiliary system characterized by the following [Desmet 1998]:

- Defective remodeling of the ductal plate (ductal plate malformation; DPM)
- Abnormal branching of the intrahepatic portal veins
- 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 dilatations of the intrahepatic biliary ducts CHF associated with macroscopic liver cysts in continuity with the bile ducts, sometimes referred to as Caroli syndrome (CS)

  Note: Caroli disease (CD), which is much rarer than CS, refers to liver cysts contiguous with the biliary tree without CHF [Caroli 1973, Summerfield et al 1986]. Given that CS and CD may coexist in different members of the same family [Caroli 1973], these probably represent a continuum.

Characteristic clinical features of CHF include the following:

- Large and abnormally shaped liver with the left lobe palpable below the xiphoid and the right lobe typically non-palpable
- Increased echogenicity of the liver parenchyma with or without macrocysts on ultrasound examination, often in the presence of relatively well-preserved hepatocellular function

- Portal hypertension (PH) resulting in splenomegaly, hypersplenism, and gastroesophageal varices

Note: Although all individuals with CHF have DPM detectable by liver biopsy at birth, abnormal liver echogenicity and splenomegaly may not be detectable during early childhood because portal fibrosis and portal hypertension (PH) are time-dependent pathologies that develop and progress with age.

Other clinical features of CHF can include recurrent cholangitis, especially when CS is part of CHF.

The severity and rate of progression of CHF and its complications vary widely even within the same family.

Portal hypertension (PH), strictly defined as an increase in the portal venous pressure leading to clinical sequelae, is the predominant manifestation of CHF [Kerr et al 1978, Summerfield et al 1986]. PH in CHF is caused by an increase in resistance to blood flow in the liver itself and is thought to be caused by congenital vascular abnormalities as well as progressive fibrosis.

In general, as hepatic fibrosis increases and PH worsens, the spleen increases 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 for bleeding increases [Kerr et al 1978, Summerfield et al 1986, Fonck et al 2001]. Variceal bleeding can occur at any age starting from infancy; however, significant PH takes time to develop and most commonly occurs in older children and adults.

Pulmonary hypertension (portopulmonary hypertension) and vascular shunts in the pulmonary parenchyma (hepatopulmonary syndrome) are complications of PH that can also be rarely seen in CHF.

Other complications of PH including ascites and encephalopathy are less common in CHF than in cirrhosis. Furthermore, individuals with CHF rarely manifest other systemic features associated with chronic liver disease, such as gynecomastia and enlarged parotid gland, with the exception of spider angiomata [Kerr et al 1978, Summerfield et al 1986, Fonck et al 2001].

Although the liver disease in individuals with CHF/CS is usually asymptomatic, the risk is increased for cholangitis and, less commonly, biliary stone formation and cholangiocarcinoma, which can develop at a relatively young age [Kerr et al 1978, Summerfield et al 1986, Fonck et al 2001].

No prospective studies of the natural history of CHF have been published. A recent thorough review of the literature evaluated a total of 1230 individuals with CHF who had been published in 155 articles [Srinath & Shneider 2012]. A majority (64%) of the cases were classified as ARPKD/CHF and 9.5% were diagnosed as isolated CHF. Follow-up time ranged from 0 to 38 years with a mean of 7.5 years. Most affected individuals were diagnosed in childhood and sequelae of portal hypertension was the predominant reported finding (409 affected individuals). Of those with portal hypertension 164 had varices, 74 of whom had bled and 81 of whom had portosystemic shunting performed. Cholangitis was reported in 152 affected individuals and was fatal in three out of 23 persons who had undergone renal transplantation. Twenty-one affected individuals were reported to have had hepatobiliary cancers, 19 of whom had cholangiocarcinoma. The youngest reported individual with hepatobiliary cancer was age 33 years. The mean age of diagnosis for cholangiocarcinoma was 60.1 years.

Most other reports on the natural history of CHF include small numbers of individuals with advanced CHF and an undetermined type of renal disease. Whether the manifestations or rate of progression of CHF differ according to the associated genetic disorder has not been determined (see Causes of Congenital Hepatic Fibrosis). Although the manifestations of non-cirrhotic PH and the complications of the bile duct abnormalities associated with autosomal recessive polycystic kidney disease (ARPKD)/CHF are well recognized, the variability in progression of CHF, even within the same family, makes prognostication difficult [Adeva et al 2006].

Factors that could exacerbate or accelerate fibrosis include excessive alcohol intake, steatohepatitis, hepatotoxic medicines, and viral hepatitis.

Establishing the Diagnosis of Congenital Hepatic Fibrosis

Ultrasound examination, the most informative diagnostic modality, often reveals:

- Increased echogenicity of the liver;
- Cysts in the hepatic parenchyma [Premkumar et al 1988, Akhan et al 2007];
- Enlarged spleen;
- Accompanying fibrocystic changes in the kidneys.

Standard-resolution ultrasound examination is sufficient to evaluate the liver and spleen; in the authors' experience high-resolution ultrasound using a 5-7 MHz probe is superior to standard-resolution ultrasound to diagnose mild renal cystic disease [Gunay-Aygun et al 2010a].

MRI including magnetic resonance cholangiopancreatography (MRCP) [Jung et al 1999, Brancatelli et al 2005] typically shows:

- Cystic or fusiform dilatations and irregularities of the intrahepatic bile ducts;
- Abnormally large left lobe of the liver extending anteriorly under the xiphoid and to the left over the spleen;
- Fusiform dilation of the extrahepatic bile ducts;
- Elongation of the gall bladder;
- Enlarged spleen, which can be quantified by calculating volume;
- Accompanying fibrocystic changes in the kidneys.

Because of the common association of renal disease with CHF and CS, many individuals with CHF have already undergone a renal evaluation.

The ultrasound and MRI findings described are highly suggestive of CHF, especially in the context of the following renal findings, which comprise the hepatorenal fibrocystic diseases (FCDs):

- Polycystic kidney disease (PKD). Inherited cystic degeneration of both kidneys associated with progressive decline in renal function and hypertension in most affected individuals. Autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD) are the most common types of PKD.
- Glomerulocystic kidney disease and diffuse cystic dysplastic kidneys
- The spectrum of tubulointerstitial disorders that includes the following:
  - Nephronophthisis (NPHP), characterized by normal-size or small kidneys with increased echogenicity on renal ultrasound examination. Renal cysts typically occur after onset of end-stage renal disease (ESRD) and localize primarily at the corticomedullary junction. Before the onset of ESRD individuals with NPHP tend to maintain blood pressure in the normal range.
  - Chronic tubulointerstitial disease, characterized histologically by renal tubular atrophy and tubulointerstitial fibrosis with relative sparing of glomerular and vascular structures
  - Urine-concentrating defect, the earliest and mildest manifestation of kidney involvement in FCDs. The urine-concentrating defect results from abnormal regulation of free water absorption in the collecting ducts and manifests as polyuria and polydipsia.
- Medullary sponge kidney. A radiologic term referring to microcystic dilatations of the renal collecting ducts observed on contrast imaging such as intravenous pyelography. A subset of individuals with medullary sponge kidney develop medullary nephrocalcinosis (radiologically demonstrable renal parenchymal calcification).

Note: Nephrocalcinosis is different from nephrolithiasis (renal stones), in which calcification is within the lumen of the collecting system or ureter.

Liver biopsy reveals the following characteristic abnormalities associated with DPM:

- Abundant, abnormally formed bile ducts in the portal tracts caused by an excess of embryonic bile duct structures remaining in their primitive ductal plate configuration [Desmet 1998] (often incorrectly described as "bile duct proliferation")
- Abnormal branching of the portal vein
- Periportal fibrosis without inflammation
- Portal-portal bridging fibrosis (i.e., not the portal tract to central vein bridging that is typical of cirrhosis)
- Multiple bile duct hamartomas (von Meyenburg complexes) within dense fibrous stroma
- Inspissated bile in the lumen of some ducts

Note: The hepatic parenchyma is normal without intrahepatic cholestasis or disruption of the hepatocellular plates.

Histopathologic findings on liver biopsy are the gold standard for diagnosis of CHF. However, liver biopsy is not required in most individuals (especially those with fibrocystic renal disease) because the diagnosis can be established on clinical findings alone [Fonck et al 2001, Gunay-Aygun et al 2010b, Gunay-Aygun et al 2013].

Differential Diagnosis of Congenital Hepatic Fibrosis

Cirrhosis. CHF is often confused with cirrhosis because of the extensive fibrosis seen on biopsy and PH seen in CHF. A distinguishing feature of CHF and non-cirrhotic PH in general is preserved hepatic synthetic function [Sarin & Kumar 2006, Gunay-Aygun et al 2013].

Diseases of the bile ducts that can lead to cirrhosis include primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [Kumagi et al 2008, Maggs & Chapman 2008]. However, both of these diseases are unusual in childhood, have significant elevation of the hepatic enzymes ALP and GGT (less common in CHF), and do not have the same appearance as CHF on imaging. Neither PBC nor PSC is associated with hepatic cystic disease.

- In PBC the anti-mitochondrial antibody is positive in most individuals; this is not the case in CHF.
- Like CHF, PSC is often associated with cholangitis. Furthermore, the bile duct strictures and dilations often seen in PSC may be mistaken for the dilated extrahepatic bile ducts of CHF and even the intrahepatic cysts of CHF.

Other causes of cirrhosis, such as viral hepatitis, alcohol-related liver disease, autoimmune hepatitis, alpha 1 antitrypsin deficiency, Wilson disease, and *HFE*-associated hereditary hemochromatosis, are distinguished based on history and laboratory testing.

Non-cirrhotic portal hypertension may be more difficult to distinguish from CHF than cirrhotic PH and relies on medical history, physical examination, laboratory testing, and imaging [Sarin & Kumar 2006]. The causes of non-cirrhotic PH are often divided into prehepatic (e.g., portal vein thrombosis), intrahepatic (e.g., schistosomiasis, nodular regenerative hyperplasia), and post-hepatic (e.g., right-sided heart failure). Liver biopsy is often needed to identify intrahepatic causes of non-cirrhotic PH.

Hepatic cysts, especially when few and small, may be a normal variant; the frequency of benign hepatic cysts increases with age.

The hepatic cysts seen in autosomal dominant polycystic liver disease, a distinct genetic disorder, may also lead to PH, but they are not typically associated with CHF and can be distinguished from cysts associated with CHF by the large number of cysts and the extent of involvement of the hepatic parenchyma [Drenth et al 2005].

Caroli disease (CD) is a congenital disorder of the liver characterized by cystic dilation of the intrahepatic bile ducts without CHF [Caroli 1973]. The diagnosis of CD relies on imaging studies. Given that CS, the association of CHF and macroscopic liver cysts in continuity with the bile ducts, and CD may coexist in different members of the same family [Caroli 1973], CS and CD probably represent a continuum.

Malignant liver disease. The multiple bile duct hamartomas of a von Meyenburg complex may be misdiagnosed as biliary cystadenoma and cystadenocarcinoma.

CHF without renal fibrocystic disease. CHF associated with chronic diarrhea and failure to thrive, hypoglycemia, and protein-losing enteropathy with coagulopathy suggests congenital disorder of glycosylation type Ib (CDG-Ib) (see Congenital Disorders of Glycosylation Overview). Analysis of serum transferrin glycoforms by isoelectric focusing and subsequent measurement of mannose phosphate isomerase enzyme activity in white blood cells is recommended for specific diagnosis.

Prevalence of the Congenital Hepatic Fibrosis

No prevalence data exist for CHF. However, based on the prevalence of various specific ciliopathies associated with CHF, the prevalence can be estimated at one in 10,000 to 20,000.

Causes of Congenital Hepatic Fibrosis

Congenital hepatic fibrosis/Caroli syndrome (CHF/CS) can rarely be an isolated finding; the gene(s) in which mutation causes isolated CFF/CS are unknown.

Most frequently CHF/CS is associated with ciliopathies (disorders of the primary cilia) that have associated renal disease: PKD, NPHP, and chronic tubulointerstitial disease, collectively referred to as the hepatorenal FCDs [Summerfield et al 1986, Gunay-Aygun 2009].

The ciliopathies are caused by defects of proteins that reside on the cilia or its basal body structures [Fliegauf et al 2007]. The ciliopathies include defects of both the primary (immotile) cilia and the respiratory (motile) cilia. It is the primary cilia, not the motile cilia, that are involved in the hepatorenal FCDs. Primary cilia, one-per-cell antenna-like organelles present on most eukaryotic cells, sense extracellular chemical and mechanical stimuli (e.g., fluid flow) and host important developmental signaling pathways such as sonic hedgehog and Wnt. Intact primary cilia-based signaling is required to ensure normal development and maintenance of the bile ducts and renal tubules.

The hepatorenal FCDs are discussed in Table 1. Note: Kartagener syndrome, a ciliopathy of the motile cilia characterized by recurrent sinopulmonary infections, right-left sidedness defects, and infertility is not associated with hepatorenal FCD and therefore not discussed here (see Primary Ciliary Dyskinesia).

Autosomal recessive polycystic kidney disease (ARPKD). Most individuals with ARPKD present in the neonatal period with enlarged echogenic kidneys. At initial presentation, fewer than half of infants have liver abnormalities, including hepatomegaly, dilated intrahepatic (and occasionally extrahepatic) biliary ducts, and mildly increased echogenicity. Approximately 30% of affected infants die in the neonatal period or within the first year of life primarily of respiratory insufficiency or superimposed pulmonary infections. More than 50% of affected children progress to end-stage renal disease (ESRD), usually in the first decade of life. With neonatal respiratory support and renal replacement therapies, the ten-year survival of those who live beyond the first year of life has improved to 82%. Fifteen-year survival is estimated at 67%-79%, and may be improving. A minority of individuals present in older childhood or young adulthood with hepatosplenomegaly and evidence of portal hypertension. Advanced CHF can contribute to post-renal transplantation complications in ARPKD [Davis et al 2003]. ARPKD is not associated with abnormalities in other organ systems. Click here for additional information on ARPKD /CHF.

Meckel syndrome (MKS) is a perinatal lethal disorder characterized by renal cystic dysplasia, CHF, postaxial polydactyly, and occipital encephalocele or other central nervous system abnormalities [Khaddour et al 2007]. CHF has been identified in all individuals with MKS who have undergone liver biopsy. MKS is genetically heterogeneous and has significant overlap with Joubert syndrome and related disorders (JSRDs) and Bardet-Biedl syndrome (BBS) [Bergmann et al 2008, Tallila et al 2008].

Nephronophthisis (NPHP), part of the spectrum of the tubulointerstitial disorders, manifests initially as a urine-concentrating defect and anemia before progressing to ESRD in childhood in most individuals [Hildebrandt & Zhou 2007, Otto et al 2008, Salomon et al 2009]. In the infantile, juvenile, and adolescent forms of NPHP the median ages for ESRD are one, 13, and 19 years, respectively. Juvenile NPHP, the most common form, typically manifests between ages four and six years with polyuria, polydipsia, and anemia. Blood pressure is typically normal in juvenile NPHP before the onset of renal failure. Juvenile NPHP accounts for 5%-10% of ESRD in children. Approximately 10%-20% of individuals with NPHP have central nervous system and/or ocular involvement that includes structural cerebellar and midbrain abnormalities overlapping with JSRD and retinal degeneration (Senior-Løken syndrome).

Renal ultrasound examination shows normal size or small kidneys with increased echogenicity. In rare cases of infantile NPHP, kidney size may be enlarged. Renal cysts in NPHP are secondary, typically occurring after ESRD develops and localizing primarily at the corticomedullary junction.

Joubert syndrome and related disorders (JSRDs)

Joubert syndrome is characterized by three primary findings: a distinctive cerebellar and brain stem malformation (the molar tooth sign [MTS]), hypotonia, and developmental delays. Often these findings are accompanied by episodic tachypnea or apnea and/or atypical eye movements. In general, the breathing abnormalities improve with age, truncal ataxia develops over time, and acquisition of gross motor milestones is delayed. Cognitive abilities are variable, ranging from severe intellectual disability to normal. The designation Joubert syndrome and related disorders (JSRD) is used to describe individuals with JS who have additional findings including retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Both intra- and interfamilial variation are seen. Some individuals with JSRD have clinically symptomatic CHF. Joubert syndrome is genetically heterozygous, with more than 20 genes identified to date.

The term **JSRDs** includes conditions that share the molar tooth sign and the clinical features of Joubert syndrome in addition to other manifestations that may represent a distinct syndrome.

JSRDs include:

- COACH syndrome. COACH is a mnemonic for *c*erebellar vermis hypoplasia, *o*ligophrenia, *a*taxia, *c*oloboma, and *h*epatic fibrosis [Foell et al 2002].
- Senior-Løken syndrome. Severe retinal degeneration with NPHP. Senior-Løken syndrome is characterized by NPHP and severe retinal degeneration.

  Note: Sometimes the severe retinal degeneration of Senior-Løken syndrome is erroneously attributed to Leber congenital amaurosis, a disorder that affects the retina only and can be caused by pathogenic variants in at least 17 different genes.

Bardet-Biedl syndrome (BBS) is characterized by cone-rod dystrophy(>90%), truncal obesity (72%), postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal dysfunction. The visual prognosis for children with BBS is poor. Night blindness is usually evident by age seven to eight years; the mean age of legal blindness is 15.5 years. Birth weight is usually normal, but significant weight gain begins within the first year and becomes a lifelong issue for most individuals.

A majority of individuals have significant learning difficulties but only a minority have severe impairment on IQ testing. Renal disease is a major cause of morbidity and mortality

Cranioectodermal dysplasia (CED) (Sensenbrenner syndrome) is characterized by abnormal bone growth (dolichocephaly, rhizomelic shortening of extremities, narrow rib cage, and decreased bone density), dental and nail dysplasia, and progressive tubulointerstitial nephritis resulting in ESRD in early childhood [Zaffanello et al 2006]. Retinal dystrophy has been reported in a few patients.

Ellis-van Creveld syndrome (EVC) is characterized by abnormal bone growth (disproportionate short stature with short limbs and ribs), congenital heart disease (most commonly an atrioventricular septal defect), postaxial polydactyly, dystrophic nails and teeth, and retinal degeneration.

Jeune asphyxiating thoracic dystrophy (JATD) is characterized by abnormal bone growth resulting in short stature, small thoracic cage and hypoplastic lungs, chronic tubulointerstitial nephritis, and CHF [Hudgins et al 1992]. Death in infancy is common, usually as a consequence of respiratory insufficiency. Most individuals with JATD who survive infancy develop retinal dystrophy and renal failure as a result of chronic tubulointerstitial nephritis. CHF is a consistent finding in autopsy and liver biopsy specimens. Individuals with JATD who are evaluated for liver disease have CHF associated with significantly elevated levels of liver enzymes ALT, AST, and GGT.

Renal-hepatic-pancreatic dysplasia (RHPD) is characterized by cystic dysplastic kidneys, DPM of the liver, and fibrocystic dysplasia of the pancreas [Sergi et al 2000, White et al 2000, Zaffanello et al 2006]. Partial or total *situs inversus* may be seen; however, the presence of situs anomalies is expected in only a subset of affected individuals because the defective nodal ciliary function results in random determination of sidedness associated with normal sidedness 50% of the time. RHPD is usually fatal in the perinatal period. Clinical variability is considerable. *NPHP3* is the first gene known to be associated with renal-hepatic-pancreatic dysplasia [Bergmann et al 2008].

Oral-facial-digital syndrome type 1 (OFD1) is associated with dysfunction of primary cilia and is characterized by the following abnormalities:

- Oral. Lobed tongue, hamartomas or lipomas of the tongue, cleft of the hard or soft palate, accessory gingival frenulae, hypodontia, and other dental abnormalities
- Facial. Widely spaced eyes or telecanthus, hypoplasia of the alae nasi, median cleft or pseudocleft upper lip, micrognathia
- Digital. Brachydactyly, syndactyly of varying degrees, and clinodactyly of the fifth finger; duplicated hallux (great toe); preaxial or postaxial polydactyly of the hands
- Brain. Intracerebral cysts, corpus callosum agenesis, cerebellar agenesis with or without Dandy-Walker malformation
- Kidney. Polycystic kidney disease
- Liver/pancreas. Cystic abnormalities of intrahepatic biliary system and pancreatic cysts [Chetty-John et al 2010]

As many as 50% of individuals with OFD1 have some degree of intellectual disability, which is usually mild. Almost all affected individuals are female. However, males with OFD1 have been described, mostly as malformed fetuses delivered by women with OFD1.

Autosomal dominant polycystic kidney disease (ADPKD) is generally a late-onset multisystem disorder characterized by bilateral renal cysts; cysts in other organs including the liver, seminal vesicles, pancreas, and arachnoid membrane; vascular abnormalities including intracranial aneurysms, dilatation of the aortic root, and dissection of the thoracic aorta; mitral valve prolapse; and abdominal wall hernias. Renal manifestations include

hypertension, renal pain, and renal insufficiency. Approximately 50% of individuals with ADPKD have end-stage renal disease (ESRD) by age 60 years.

The prevalence of liver cysts, the most common extrarenal manifestation of ADPKD, increases with age and may have been underestimated by ultrasound and CT studies. The prevalence of intracranial aneurysms is higher in those with a positive family history of aneurysms or subarachnoid hemorrhage (22%) than in those without such a family history (6%). Mitral valve prolapse, the most common valvular abnormality, occurs in up to 25% of affected individuals. Substantial variability in severity of renal disease and other extrarenal manifestations occurs even within the same family.

In ADPKD hepatic cysts are not usually associated with CHF or PH; however, 19 affected individuals from 14 families with ADPKD have well-documented CHF and PH [Tazelaar et al 1984, Lee & Paes 1985, Cobben et al 1990, Matsuda et al 1990, Lipschitz et al 1993, Chait et al 1994, Kaczorowski et al 2001, O'Brien et al 2012]. Three of these families, evaluated at the NIH, had pathogenic variants in *PKD1;* sequencing of *PKHD1* as a potential modifier did not reveal any pathogenic variants [O'Brien et al 2012]. O'Brien et al [2012] tabulated the characteristics of all 19 individuals with ADPKD-CHF (9 boys, 10 girls); the characteristics of CHF in ADPKD were similar to those of CHF in ARPKD. Portal hypertension was the main manifestation of CHF, hepatocellular function was preserved, and liver enzymes were largely normal. In all of the 14 families, CHF was not inherited vertically; that is, the parents of the index cases had PKD but did not have CHF, suggesting the influence of a modifier gene or genes. Given that both boys and girls are affected, the modifier gene(s) are likely located on autosomal chromosomes and are less likely to be X-linked.

Table 1. Molecular Genetics of the Hepatorenal Fibrocystic Diseases

MOI	Disease Name	Locus Name	Gene
AR	ARPKD	PKHD1	*PKHD1*
	Nephronophthisis [1]	NPHP1 [2]	*NPHP1*
		NPHP2	*INVS*
		NPHP3	*NPHP3*
		NPHP4	*NPHP4*
		NPHP5 (SLSN5)	*IQCB1*
		NPHP6 [3] (SLSN6)	*CEP290*
		NPHP7	*GLIS2*
		NPHP8 [4]	*RPGRIP1L*
		NPHP9	*NEK8*
		NPHP11	*TMEM67*
		NPHP12	*TTC21B*
		NPHP13	*WDR19*
		NPHP14	*ZNF423*
		NPHP15	*CEP164*
		NPHP16	*ANKS6*
	Joubert syndrome and related disorders [5]	JBTS1	*INPP5E*
		JBTS2	*TMEM216*
		JBTS3	*AHI1*

Table 1. continued from previous page.

MOI	Disease Name	Locus Name	Gene
		JBTS4 [2]	*NPHP1*
		JBTS5 [3]	*CEP290*
		JBTS6 [6]	*TMEM67*
		JBTS7 [4]	*RPGRIP1L*
		JBTS8	*ARL13B*
		JBTS9	*CC2D2A*
		JBTS10	*OFD1*
		JBTS11	*TTC21B*
		JBTS12	*KIF7*
		JBTS13	*TCTN1*
		JBTS14	*TMEM237*
		JBTS15	*CEP41*
		JBTS16	*TMEM138*
		JBTS17	*CPLANE1*
		JBTS18	*TCTN3*
		JBTS19	*ZNF423*
		JBTS20	*TMEM231*
			TCTN2
	Bardet-Biedl syndrome [7]	BBS1	*BBS1*
		BBS2	*BBS2*
		BBS3	*ARL6*
		BBS4	*BBS4*
		BBS5	*BBS5*
		BBS6	*MKKS*
		BBS7	*BBS7*
		BBS8	*TTC8*
		BBS9	*BBS9*
		BBS10	*BBS10*
		BBS11	*TRIM32*
		BBS12	*BBS12*
		BBS13 [8]	*MKS1*
		BBS14 [3]	*CEP290*

Table 1. continued from previous page.

MOI	Disease Name	Locus Name	Gene
	Meckel syndrome [9]	MKS1 [8]	*MKS1*
		MKS2	*TMEM216*
		MKS3 [5]	*TMEM67*
		MKS4 [3]	*CEP290*
		MKS5 [4]	*RPGRIP1L*
		MKS6	*CC2D2A*
		MKS7	*NPHP3*
		MKS8	*TCTN2*
		MKS9	*B9D1*
		MKS10	*B9D2*
		MKS11	*TMEM231*
	Cranioectodermal dysplasia		*IFT122*
	Ellis-van Creveld syndrome	EVC [10]	*EVC*
			EVC2
	Jeune asphyxiating thoracic dystrophy	JATD1	Unknown
		JATD2	*IFT80*
	Renal-hepatic-pancreatic dysplasia		*NPHP3*
XL	OFD1		*OFD1*
AD	ADPKD	PKD1	*PKD1*
		PKD2	*PKD2*

AD = autosomal dominant; ADPKD = autosomal dominant polycystic kidney disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; MOI = mode of inheritance; XL = X-linked

1. See Nephronophthisis: Phenotypic Series to view genes associated with this phenotype in OMIM.

2. Locus names for *NPHP1* include: NPHP1, JBTS4.

3. Locus names for *CEP290* include: NPHP6 (SLSN6), JBTS5, BBS14, MKS4. *CEP290* pathogenic variants result in phenotypes ranging from Leber congenital amaurosis (in which only the retina is involved) to typical perinatal lethal MKS [Baala et al 2007, Helou et al 2007].

4. Locus names for *RPGRIP1L* include: NPHP8, JBTS7, MKS5

5. See Joubert Syndrome: Phenotypic Series to view genes associated with this phenotype in OMIM.

6. Locus names for *TMEM67* include: NPHP11, JBTS6, MKS3

7. See Bardet-Biedl Syndrome: Phenotypic Series to view genes associated with this phenotype in OMIM.

8. Locus names for *MKS1* include: BBS13, MKS1

9. See Meckel Syndrome: Phenotypic Series to view genes associated with this phenotype in OMIM.

10. EVC and *EVC2* lie in a head-to-head configuration at the same locus.

Phenotypic Features Shared by the Hepatorenal Fibrocystic Diseases

The most common phenotypic features of the hepatorenal FCDs are described here. Although each of the hepatorenal FCDs has distinct features, the clinical findings and the associated genes overlap in several (see Table 1):

- CHF is a constant finding in ARPKD and MKS; it occurs with variable frequencies in JSRDs, BBS, OFD1, EVC, JATD, and RHPD.

- Developmental abnormalities of the mid/hindbrain that range from Dandy-Walker variant/mega cisterna magna to occipital encephalocele (as in JSRDs and MKS) are the second most common manifestation in the hepatorenal FCDs [Badano et al 2006].
- Retinal degeneration, resulting from involvement of the connecting cilia of the photoreceptor cells that are specialized primary cilia of the retina, is a common manifestation of the hepatorenal fibrocystic diseases [Adams et al 2007]. Retinal degeneration is observed consistently in BBS, Senior-Løken syndrome, and a subset of individuals with JSRDs.
- Polydactyly, seen with variable frequencies in many ciliopathies including MKS, BBS, OFD1, and JSRDs, is mostly postaxial and can involve upper and lower extremities.
- Right-left sidedness defects (lateralization defects, *situs inversus*) are seen in some disorders of the primary cilia (e.g., BBS and RHPD). The situs abnormalities may result in complete or partial reversal of internal organs including lungs, heart, liver, gastrointestinal tract, and spleen. In RHPD the lateralization defects include the so-called polysplenia/asplenia syndromes. The presence of lateralization defects in only some ciliopathies is likely due to the fact that only a subset of the primary cilia proteins are critical for the function of the nodal cilia of the embryo, which determine body asymmetry.

Currently, the hepatorenal FCDs are classified by phenotype; however, because of tremendous phenotypic and genetic overlap (see Table 1) between the hepatorenal FCDs, it is likely that in future the gene-based classification will be quite different from the current phenotype-based classification.

Furthermore, the large proportion of individuals with a ciliopathy (e.g., NPHP and JSRDs) with only one identified pathogenic variant and the extreme variability of the phenotype associated with pathogenic variants in some genes (e.g., *CEP290,* associated with NPHP6, JBTS5, MKS4, and Leber congenital amaurosis) suggest that some individuals with a hepatorenal fibrocystic disease may have pathogenic variants in more than one gene encoding a protein found in cilia or basal bodies.

Genotype-Phenotype Correlations

ARPKD. Most infants with severe perinatal ARPKD and CHF have two protein truncating variants in *PKHD1*. Most individuals who survive the neonatal period have at least one milder pathogenic (missense) variant [Bergmann et al 2003]. However, perinatal disease severity in ARPKD/CHF is largely determined by the extent of the kidney disease. No genotype-phenotype correlation data on *PKHD1*-related CHF exist at this time.

Evaluation Strategy

Once the diagnosis of congenital hepatic fibrosis (CHF) has been established in a proband, the following approach can be used to determine the specific cause of the CHF to aid in discussions of prognosis and genetic counseling.

Family history. A detailed three-generation family history focusing on hepatorenal fibrocystic disease, CHF/CS, liver or kidney disease of unknown etiology, and the associated findings of the multisystem disorders discussed in this *GeneReview* can be used to help determine the inheritance pattern in an individual with CHF.

- Attention to a history of consanguinity and medical problems in sibs and evaluation of any unusual findings in sibs may clarify if one of the autosomal recessive disorders discussed in Table 1 is present.
- If an autosomal recessive syndrome is not identified in the proband and/or the findings and/or family history suggest autosomal dominant inheritance, ultrasound examination of parents and sibs to evaluate for the presence of asymptomatic kidney and/or liver disease characteristic of ADPKD is useful even in the absence of a positive family history.

Physical examination. The presence of other findings including the following may suggest a specific diagnosis: PKD, NPHP, tubulointerstitial nephritis, medullary nephrocalcinosis, medullary sponge kidney, or urine

concentration defect in normal appearing kidneys; retinopathy; ocular coloboma; oculomotor apraxia; speech apraxia; mid/hindbrain abnormalities ranging from nonspecific posterior fossa abnormalities such as enlarged basilar cisterns or Dandy-Walker variant to classic MTS; developmental delay; oral anomalies; polydactyly; obesity; *situs inversus*; and short stature or other abnormalities suggesting a skeletal dysplasia.

Testing

Other evaluations including kidney function tests, echocardiogram, skeletal survey, complete eye examination, and brain MRI may be useful to establish the specific hepatorenal fibrocystic disease associated with CHF based on the abnormalities identified on family history and physical examination.

Molecular genetic testing. Although the clinical diagnosis of a specific hepatorenal FCD guides molecular genetic testing, some unique aspects of hepatorenal FCD in general may complicate the diagnostic approach. Hepatorenal FCDs are genetically heterogeneous and share significant overlap in phenotype and associated genes: NPHP is associated with pathogenic variants in 15 genes, JSRDs 20 genes, BBS 14 genes, and MKS 11 genes (see Table 1).

In typical ARPKD/CHF, the diagnosis is often made on clinical findings; however, molecular genetic testing of *PKHD1* is being increasingly performed, especially in individuals with atypical findings.

In individuals with MKS who are of European origin, testing for the 29-bp IVS15-7_35 deletion in *MKS1* should be prioritized [Auber et al 2007]. Testing of *MKS1* and *TMEM67* may be prioritized based on phenotype (see Causes, Meckel syndrome).

Multigene panel. An alternative to single-gene or sequential testing for molecular diagnosis of a proband suspected of having a diagnosis associated with congenital hepatic fibrosis is use of a multigene panel.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The syndromes associated with congenital hepatic fibrosis (CHF) can be inherited as a multisystem disorder in an autosomal dominant, autosomal recessive, or X-linked recessive manner. Genetic counseling depends on accurate determination of the specific genetic diagnosis.

CHF is rarely an isolated finding; the gene(s) in which mutation resulting in isolated CHF occurs are unknown.

Empiric Risks to Family Members – Isolated CHF

Parents, sibs, offspring of a proband. No data on the empiric risk to parents, sibs, or offspring of an individual with isolated CHF (i.e., not a part of a syndrome) are available.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. CHF is typically one of several findings in an individual with a specific syndrome. Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for congenital hepatic fibrosis are possible.

Ultrasound examination

- The echogenicity of the fetal liver in individuals with the hepatorenal FCDs discussed in this *GeneReview* is not identified on prenatal ultrasound examination.
- In most cases of hepatorenal FCDs, prenatal ultrasound examination is more likely to show findings associated with renal disease than with liver disease (including hyperechoic kidneys that are either enlarged or normal size and oligohydramnios) or to show findings of associated malformations such as polydactyly, posterior encephalocele, cerebellar hypoplasia, or other central nervous system anomalies, oral clefts, or abnormalities of bone growth.
- In rare instances of prenatal onset of CS, fetal liver cysts can be visualized on ultrasound examination.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **ARPKD/CHF Alliance**
  PO Box 70
  Kirkwood PA 17536
  Phone: 800-708-8892 (toll-free); 717-529-5555
  Fax: 800-807-9110 (toll-free)
  Email: info@arpkdchf.org
  www.arpkdchf.org

- **American Liver Foundation**
  75 Maiden Lane
  Suite 603
  New York NY 10038
  Phone: 800-465-4837 (Toll-free HelpLine); 212-668-1000
  Fax: 212-483-8179
  Email: info@liverfoundation.org
  www.liverfoundation.org

- **Children's Liver Disease Foundation (CLDF)**
  36 Great Charles Street
  Birmingham B3 3JY

United Kingdom
Phone: +44 (0) 121 212 3839
Fax: +44 (0) 121 212 4300
Email: info@childliverdisease.org
www.childliverdisease.org

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital hepatic fibrosis (CHF), the following evaluations are recommended:

- Complete blood count, hepatic panel, and coagulation profile and ultrasound examination to identify mild, moderate, or severe portal hypertension (PH), hypersplenism, and biliary tree abnormalities [Lonergan et al 2000]
- Esophago-gastro-duodenoscopy (EGD) to screen for varices, particularly when the platelet count has decreased significantly over time or prior to interventions such as renal transplantation [Garcia-Tsao et al 2007, Bosch et al 2008]. Although not universally accepted in children, screening for varices allows for prognostication, planning, and primary prevention of variceal bleeding.
- Screening for hepatopulmonary syndrome by measuring upright oxygen saturation and screening for portopulmonary hypertension with echocardiogram to estimate pulmonary artery pressure [Whitworth & Sokol 2005]
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

There is no known treatment for the underlying defect in CHF: no therapies can repair the primary ductal plate malformation or reverse the fibrosis or biliary tree abnormalities. Therapies based on extrapolations from other forms of liver disease, anecdotal reports, and deductive reasoning are used to manage the complications of the underlying defect [Shneider & Magid 2005].

The most important manifestations of CHF are variceal bleeding, hypersplenism, cholangitis and, to a lesser extent, biliary stones, cholangiocarcinoma, and hepatocellular carcinoma.

Variceal bleeding. The management of varices has been reviewed [Shneider & Magid 2005, Garcia-Tsao et al 2007, Bosch et al 2008, Ling et al 2011, Shneider et al 2012]. Care should be provided by those experienced in the management of PH.

Primary prevention (prior to any variceal bleeding) entails screening for varices and treating medium or large varices with nonselective beta blockers with the dose titrated to pulse and blood pressure. If beta blockers are not tolerated, variceal banding should be considered. Management in children is not as well defined as in adults. Affected children should be referred to tertiary centers with experience in the management of varices in children.

Standard procedures for management of variceal bleeding include obtaining adequate initial intravenous access, resuscitation, transfusion without over transfusion, octreotide, antibiotic prophylaxis, proton pump inhibition, and endoscopy when stabilized.

Secondary prevention of variceal bleeding (once bleeding has already occurred) consists of banding of esophageal varices, histacryl injection of gastric varices, and continued use of nonselective beta blockers.

Because banding devices do not fit on the smallest endoscopes, small children with variceal bleeding often undergo sclerotherapy instead.

Individuals who have had repeated variceal bleeding (especially if gastric varices are present) should be considered for surgical portosystemic shunting rather than repeated variceal ligation [Shneider & Magid 2005, Garcia-Tsao et al 2007, Bosch et al 2008]. Such intervention is best performed in a center experienced with this procedure.

Although controversial, consideration of a surgical shunt in an individual with CHF who has never had variceal bleeding may be reasonable if PH is likely to progress and liver transplantation is unlikely given the intact hepatic synthetic function in certain settings. For example, a surgical shunt would be a strong consideration in an individual with large varices that have never bled if appropriate expert care is not available for emergent management of variceal bleeding.

Transjugular intrahepatic portosystemic shunts (TIPS) are widely available. However, it is the authors' opinion that use of TIPS is not indicated outside of an emergency; because of their intrinsic occlusion rate, particularly when considered over long periods of time, TIPS may require repeated procedures to maintain adequate patency. Furthermore, the intravenous contrast often utilized to assess and perform TIPS revisions is potentially nephrotoxic – a serious consideration given the typical association of CHF with ARPKD.

Hypersplenism. Hypersplenism usually does not result in clinically significant sequelae. Individuals with significant splenomegaly are fitted with spleen guards to wear when playing contact sports or performing activities that could result in splenic injury.

Splenectomy is contraindicated because it does not treat the underlying PH and often exacerbates it.

Abnormalities of the biliary tree. Cholangitis should be considered and investigated in individuals known to have biliary dilatation who develop unexplained fever or right upper-quadrant pain with or without jaundice [Shneider & Magid 2005].

Cholangitis is best treated with rapid institution of appropriate antibiotics.

Segmental resection of the liver is a controversial option for individuals with segmental bile duct abnormalities who have had repeated episodes of cholangitis [Ulrich et al 2008] even though cysts may form in other areas of the liver after the resection.

Recurrent cholangitis with or without more widespread bile duct abnormalities is best treated with liver transplantation. If cysts in the extrahepatic bile duct are complicated by recurrent infection and/or the presence of stones, excision of the common bile duct with a Roux-en-Y hepatojejunal anastomosis has been recommended.

Biliary stones. The treatment of biliary stones depends on their location, number, and size. Care is best provided in a tertiary care facility with expertise in managing biliary stones.

Cholangiocarcinoma and hepatocellular carcinoma. These should be managed by a multidisciplinary team.

Patient education. Patients are taught the manifestations of variceal bleeding (hematemesis, melena, and hematochezia) and cholangitis (fever, abdominal pain, and jaundice) and instructed to seek appropriate care when such manifestations occur.

Prevention of Secondary Complications

The CDC (Centers for Disease Control) recommends immunization for hepatitis A and B in persons with chronic liver disease.

Although evidence is lacking, antibiotic prophylaxis for recurrent cholangitis is sometimes used in individuals who have had cholangitis [Shneider & Magid 2005].

Surveillance

General health should be closely followed. Decreased growth rate should be investigated as it is less likely to be the result of PH than of other associated problems, such as reduced renal function.

Extrapolating from studies in persons with cirrhosis, individuals with CHF should be screened for esophageal varices particularly when the platelet count decreases significantly over time or prior to interventions such as renal transplantation [Garcia-Tsao et al 2007, Bosch et al 2008]. Screening is controversial in children and should only be undertaken if a therapeutic intervention (e.g., beta-blocker therapy, variceal banding) is being considered.

- Small varices warrant a repeat esophago-gastro-duodenoscopy (EGD) in a year.
- If no varices are identified when EGD is performed because of a decline in platelet count, EGD should be repeated every two to three years.

Screening for hepatopulmonary syndrome is achieved by measuring upright oxygen saturation; screening for portopulmonary hypertension is performed with echocardiogram to estimate pulmonary artery pressure [Whitworth & Sokol 2005] in the presence of sustained platelet decrease and/or prior to an intervention.

Imaging allows for:

- Assessment of spleen size to indirectly follow PH;
- Visualization of bile duct abnormalities (e.g. cysts in the liver) that could identify individuals at greater risk for cholangitis, bile duct stones, and cholangiocarcinoma.

The appropriate frequency of surveillance imaging is not well defined, and depends on disease severity. For individuals with mild disease, ultrasound examination every two years would be adequate; for those with more severe disease, an annual ultrasound examination could enable adequate monitoring of disease progression.

Note: No data on surveillance for cholangiocarcinoma or hepatocellular carcinoma in this setting are available. However, the incidence in children is thought to be extremely rare (see Definition, Clinical Manifestations of Congenital Hepatic Fibrosis).

Agents/Circumstances to Avoid

The following agents/illnesses known to accelerate hepatic fibrosis could have the same effect in CHF and should be avoided or aggressively managed:

- Alcohol
- Obesity
- Diabetes mellitus
- Malnutrition
- Infection with human immunodeficiency virus (HIV)
- Immunosuppression (e.g., after renal transplantation)

Hepatotoxic medicines should be avoided.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in those with varices because of the risk of gastrointestinal bleeding and poor clotting as a result of impaired platelet function.

Behavior that could increase the risk of viral hepatitis should be avoided.

Contact sports, or activities that are likely to result in splenic injury, are to be avoided once the spleen is significantly enlarged.

Therapies Under Investigation

Although there are theoretic reasons why choleretics such as ursodeoxycholate may impede the development of abnormalities of the bile ducts, or even fibrosis, this has not been proven [Shneider & Magid 2005].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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Chapter Notes

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