TOPIC HIGHLIGHT

Yusuf Bayraktar, Professor, *Series Editor*

Experience of a single center with congenital hepatic fibrosis: A review of the literature

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Abstract

Congenital hepatic fibrosis (CHF) is an autosomal recessive inherited malformation defined pathologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts. It is one of the fibropolycystic diseases, which also include Caroli disease, autosomal dominant polycystic kidney disease, and autosomal recessive polycystic kidney disease. Clinically it is characterized by hepatic fibrosis, portal hypertension, and renal cystic disease. CHF is known to occur in association with a range of both inherited and non-inherited disorders, with multiorgan involvement, as a result of ductal plate malformation. Because of the similarities in the clinical picture, it is necessary to differentiate CHF from idiopathic portal hypertension and early liver cirrhosis, for which a liver biopsy is essential. Radiological tests are important for recognizing involvement of other organ systems. With regards to our experience at Hacettepe University, a total of 26 patients have been diagnosed and followed-up between 1974 and 2009 with a diagnosis of CHF. Presentation with Caroli syndrome was the most common diagnosis, with all such patients presenting with symptoms of recurrent cholangitis and symptoms related to portal hypertension. Although portal fibrosis is known to contribute to the ensuing portal hypertension, it is our belief that portal vein cavernous transformation also plays an important role in its pathogenesis. In all patients with CHF portal vein morphology should be evaluated by all means since portal vein involvement results in more severe and complicated portal hypertension. Other associations include the Joubert and Bardet-Biedl syndromes.

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INTRODUCTION

Congenital hepatic fibrosis (CHF) is an autosomal recessive inherited malformation defined pathologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts. The hepatic manifestations of CHF were first described in 1856[1]. The term CHF, with its varied clinical manifestations, was recognized in 1960[2], and later on elaborated in 1961[3]. CHF is one of the fibropolycystic diseases, which also include Caroli disease, autosomal dominant polycystic kidney disease (AD-PKD), and autosomal recessive polycystic kidney disease (ARPKD). Clinically it is characterized by hepatic fibrosis,

portal hypertension, and renal cystic disease.

The exact incidence and prevalence of CHF are not known, but it is a rare disease. By 1988, only 200 patients with CHF had been reported in the literature[4]. In most patients, the first manifestations of the disease are signs or symptoms related to portal hypertension, especially splenomegaly and varices, often with gastrointestinal bleeding[5]. The clinical manifestations of CHF are, however, nonspecific, making the diagnosis of this disorder extremely difficult. Onset of symptoms and signs is highly variable and ranges from early childhood to the 5th or 6th decade of life, although this disorder is diagnosed in most patients during adolescence or young adulthood[6]. The late appearance of symptoms and their clinical evolution suggest that CHF is a dynamic and progressive condition.

ASSOCIATED SYNDROMES

CHF occurs in association with a range of both inherited and non-inherited disorders, with multiorgan involvement (Table 1). Several gene mutations have been established for more commonly encountered conditions that have been better investigated (e.g. Joubert syndrome, Bardet-Biedl syndrome). In these conditions, hepatic fibrosis has been reported to occur to varying degrees; however, in most cases, the main cause of morbidity and mortality is involvement of other organ systems, particularly the kidneys and central nervous system. Patients rarely reach adulthood, and in many cases death occurs intrauterine or in early childhood.

PATHOPHYSIOLOGY

It has been established that congenital hepatic fibrosis, and indeed Caroli's disease closely resemble each other pathophysiologically, in that both occur as a result of ductal plate malformation. The ductal plate is a cylindrical layer of cells that surround a branch of the portal vein, and is the embryonic precursor of the intrahepatic bile ducts, as both interlobular and intralobular bile ductules develop from the ductal plate. Progressive remodeling starts at 12 wk of gestation, and full maturation is usually complete by 20 wk. Arrest of maturation and the lack of remodeling of the ductal plate that occurs as a result leads to the persistence of an excess number of immature embryonic duct structures. This abnormality has been termed the ductal plate malformation. The persistence of these immature duct elements stimulates the formation of portal fibrous tissue, and it is this periportal fibrosis that contributes to the clinical picture of recurrent cholangitis or portal hypertension and associated symptoms (Figure 1). Although long standing portal hypertension is known to result in secondary portal vein thrombosis, and eventually portal vein cavernous transformation (PVCT), it is firmly believed that PVCT is actually a component of the disorder, present at the onset rather than developing at a later stage. Embryologically speaking, the development of bile ducts and hepatic vasculature are closely related. The ductal plate malformation has been shown to be associated with a "pollard willow" malformation of the portal vein, which results in too many small and closely branched portal veins, which supports the idea that PVCT may be congenital. Histologically, enlarged portal tracts containing immature ductal plates surrounding several hypoplastic or even obliterated portal vein branches are observed[7]. In one report, PVCT was observed in almost 50% of patients with congenital hepatic fibrosis, and such patients had relatively larger splenomegaly than those without PVCT, as well as suffering from more frequent bleeding episodes from esophageal varices[8].

Furthermore, depending on the stage of arrest of maturation, either the small interlobular bile ducts (congenital hepatic fibrosis), or the medium intrahepatic bile ducts (Caroli's disease) may be involved. Involvement of both simultaneously results in what is known as Caroli's syndrome. In this context, the clinical picture of Caroli's disease (recurrent cholangitis) may be so predominant that co-existing congenital hepatic fibrosis may easily be overlooked. A liver biopsy is therefore warranted in all patients with suspected Caroli's disease to confirm the presence or absence of Caroli's syndrome[9,10].

The hepatic stellate cell (HSC) is at the center of the hepatic fibrotic process associated with liver disease, and has also been shown to play a role in the progression of the disease in congenital hepatic fibrosis. It is widely accepted that transforming growth factor (TGF)-β is a potent growth inhibitory and profibrotic cytokine which plays a pivotal role in the physiological process of wound healing as well as in the pathogenesis of organ fibrosis[11]. TGF-β expression has been shown to be increased in a wide range of fibrotic diseases. Initiation of HSC activation is primarily induced by TGF-β1 derived from Kupffer cells. TGF-β1 mediates its profibrotic actions by stimulating fibroblasts and related cell types, including the HSC in the liver, to secrete a wide range of extracellular matrix proteins. In pathological conditions this leads to accumulation of fibrotic matrix or in a more physiological context to the efficient healing of wounds[12-14]. Latent TGF-β is also activated by MMP-9, another product of Kupffer cells. TGF-β has other important actions, namely its immunomodulatory properties and its antiproliferative effects on epithelial cells, including hepatocytes.

Several studies have attempted to establish the pathophysiological mechanism behind the abnormal and excessive fibrotic response associated with CHF. Degradation of the basement membrane and extracellular matrix (ECM) constituents, and the remodeling of the ECM are important processes of embryonic development. Basal laminar components such as laminin and type IV collagen along with the coordinated expression of proteolytic enzymes are thought to be essential for the normal development of intrahepatic bile ducts[15-18]. Most of the proteolytic enzymes involved in these processes belong to the matrix metalloproteinases (MMPs) and the serine proteinases, in particular the plasminogen activator (PA)/plasmin system[19,20]. Both tissue PA (tPA) and urokinase type PA have been shown to contribute to the plasminogen-

Table 1 Syndromes with associated congenital hepatic fibrosis

Associated disorder	Genetic anomaly [chromosome (gene)]	Characteristic clinical features
Caroli syndrome	6p21.1-p12 (*PKHD1* gene)	Caroli's disease - ectasia or segmental dilatation of the larger intrahepatic ducts
Polycystic kidney disease	6p21.1-p12 (*PKHD1* gene)	Progressive cystic dilation of the renal tubule (resulting in renal failure), hepatic cysts, cerebral aneurysms, cardiac valvular abnormalities
Joubert syndrome	9q34.3; 11p12-q13; 6q23 (*AHI1* gene); 2q13 (*NPHP1* gene); 12q21.32 (*CEP290* or *NPHP6* gene); 8q21 (*TMEM67* gene); 16q12.2 (*RPGRIP1L* gene)	Cerebellar vermis hypoplasia retinitis pigmentosa, nystagmus, ataxia
Senior-Loken syndrome	2q13 (*NPHP1, NPHP4, NPHP5* genes); 3q22 (*NPHP3* gene)	Cerebellar ataxia and skeletal abnormalities, nephronophthisis, retinal dystrophy, sensorineural hearing loss
COACH syndrome	4p15.3 (*CC2D2A* gene)	Cerebellar vermis hypo/aplasia, oligophrenia, ataxia, coloboma, polydactyly
Cogan syndrome	2q13 (*NPHP1* gene)	Oculomotor apraxia, nephronophthisis, cerebellar ataxia
Arima syndrome	Not yet established	Cerebellar vermis hypoplasia, renal abnormalities, psychomotor retardation
Meckel syndrome	17q23 (*MKS1* gene); 8q (*TMEM67* gene); 12q (*CEP290* gene); 16q12.2 (*RPGRIP1L* gene); 4p15 (*CC2D2A* gene); 11q	Microcephaly, renal cystic disease, hypoplastic or ambiguous genitalia, polydactyly, congenital heart defect, cleft palate, ocular defects
Bardet-Biedl syndrome	11q13; 16q21; 3p12-q13 (*ADP-ribosylation factor* gene); 15q22.3; 2q31; 20p12 (*MKKS* gene); 4q27; 14q32.11 (*tetratricopeptide repeat domain-containing* gene); 7p14; 12q; 9q33.1; 4q27; 17q23 (*MKS1* gene); 12q21.3 (*CEP290* gene)	Rod-cone dystrophy (atypical retinitis pigmentosa), postaxial polydactyly, central obesity, mental retardation, hypogonadism, and renal dysfunction
Alstrom syndrome	2p13 (*ALMS1* gene)	Childhood obesity congenital retinal dystrophy, sensorineural hearing loss, endocrinopathies, cardiomyopathy, renal failure
Oral-Facial-Digital type IV - Mohr-Majewski syndrome	Not yet established	Lobulated tongue, pseudo-cleft of lip, hyperplastic frenula, polydactyly, severe bilateral deafness

dependent lysis of basement membrane laminin in human carcinoma cell lines. Furthermore, plasmin contributes to the activation of MMP-9 and MMP-13 which also play an important role in the degradation of basement membrane components including type IV collagen. In a recent study by Yasoshima *et al*[21], it was postulated that biliary overexpression of plasminogen and tPA leads to the generation of excessive amounts of plasmin, and subsequent plasmin dependent lysis of the ECM molecules which may contribute to biliary dysgenesis in CHF.

Overexpression of the osteopontin gene has also been implicated in the pathophysiology of biliary atresia, as well as congenital cholestatic syndromes such as CHF and Caroli's disease. Osteopontin is a stimulant of fibro-inflammation, and its overexpression has been shown to be regulated by the presence of excessive amounts of regulatory factors such as NF-κB and TGF-β1[22].

In an effort to establish how the presence of excessive immature bile ducts contributes to the process of fibrosis, Sato *et al*[23] managed to demonstrate in a rat model that in the presence of TGF-β1, cholangiocytes acquire mesenchymal features, thus resembling fibroblasts. They speculated that excess production of extracellular matrix molecules by these transformed cells may contribute to the progressive periportal/hepatic fibrosis.

On a different note, a possible role of microRNA has been postulated in the pathogenesis of fibropolycystic disorders involving both the liver and the kidneys. Chu *et al*[24] demonstrated decreases in the levels of the microRNA miR15a in the livers of patients with ARPKD, ADPKD and CHF. They reported that this resulted in an increase in the expression of a cell-cycle regulator known as cell division cycle 25A gene product (Cdc25A), which is directly responsible for cellular proliferation and cystogenesis *in vitro*.

CLINICAL PICTURE

The age of onset of presentation and the severity of symptoms varies greatly, with patients usually being diagnosed in childhood or early adulthood, although presentations as late as in the fifth decade have been reported. Although patients usually present with symptoms involving other organ symptoms (e.g. renal, central nervous system, *etc*.), cases referred for gastroenterologic/hepatologic consultation generally have complaints attributed to CHF. Four clinical forms have been defined[25]: (1) Portal hypertension (most common; more severe in the presence of portal vein abnormality); (2) Cholangitic - cholestasis and recurrent cholangitis; (3) Mixed; and (4) Latent - presentation at a late age.

Most patients are asymptomatic, while some may complain of mild right upper quadrant pain. Patients with a predominant portal hypertensive picture may present with upper gastrointestinal variceal bleeding. Physical examination findings include hepatomegaly, with predominant involvement of the left lobe, splenomegaly and nephromegaly. The liver is firm, with a mildly nodular surface. Laboratory workup may reveal mild elevations in liver enzymes. Patients with a predominantly cholangitic clinical picture may have marked elevations in alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT) and bilirubin. Varying cytopenias (leukopenia, thrombocytopenia) secondary to hypersplenism may be seen on a blood count. Abnormal renal func-
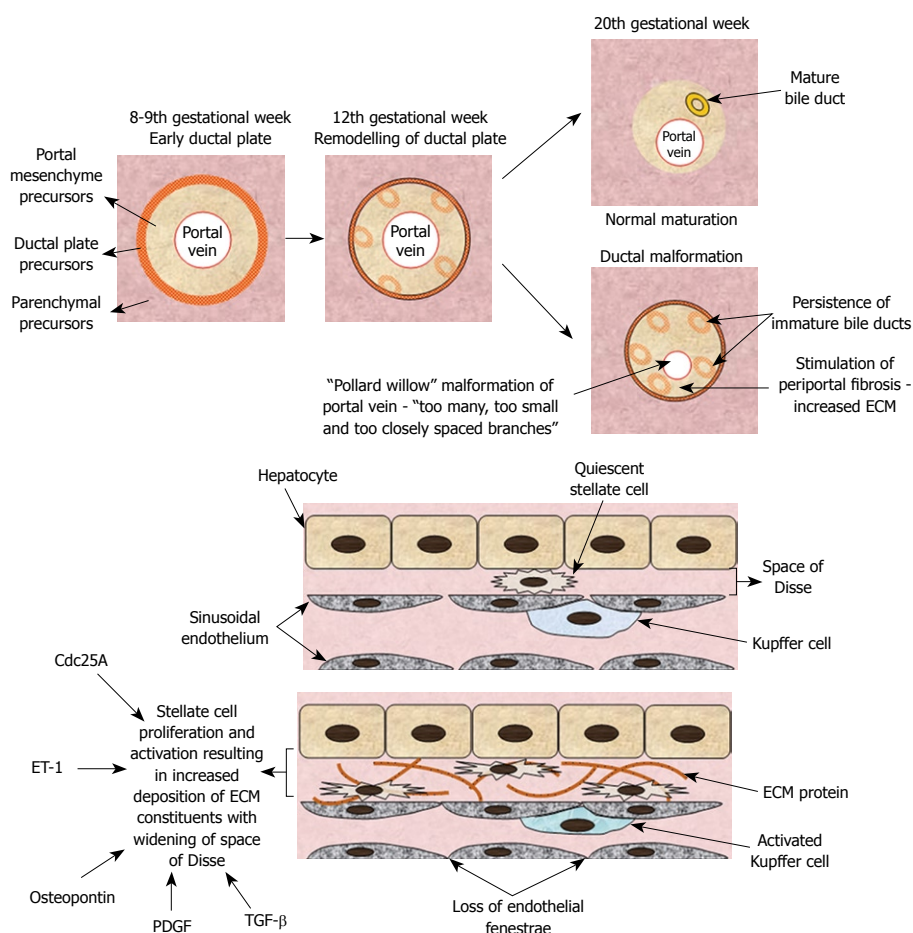
Figure 1 Pathogenesis of congenital hepatic fibrosis. Embryological and molecular perspective. ET-1: Endothelin 1; PDGF: Platelet-derived growth factor; TGF: Transforming growth factor; ECM: Extracellular matrix; Cdc25A: Cell division cycle 25A gene product (cell-cycle regulator).

tions tests are associated with extensive cystic renal disease, which may even progress to end-stage renal failure[26].

COMPLICATIONS

Cholangiocellular carcinoma

The association of cholangiocellular carcinoma (CCC) with congenital cystic malformation of the biliary tree, as seen in Caroli's disease and Caroli's syndrome, has been well established, ranging from 2.5%-16% of afflicted individuals. However, pure congenital fibrosis has also been reported to result in CCC[27,28].

DIAGNOSIS

Role of radiology

Ultrasonography (US) is generally regarded as the first line modality used in the diagnostic process with its high utility, lack of radiation exposure and its capability of detecting the bile duct and liver parenchymal abnormality. In particular, its unique capability of detecting the parenchymal heterogeneity and the associated kidney abnormalities accentuates its role in the diagnosis. Findings include hypertrophy of the left lateral segment and caudate, normal or hypertrophic left medial segment, atrophic right lobe, presence of hepatosplenomegaly, dilatation of the intrahepatic and extrahepatic bile ducts with concomitant focal cystic or solid lesions such as regenerative liver nodules and periportal thickening, dilated intrahepatic bile ducts

and stones in the ducts (Caroli's disease), hepatic and renal cysts, and portal vein cavernous transformation (Figure 2).

Computed tomography (CT) offers an advantage to US in that it provides a better depiction of gross morphology of the liver with accurate volume measurements and imaging of liver vasculature, as well as demonstrating any changes in the biliary tree (Figure 3A and B). Periportal cuffing, indicative of the fibrotic process, may also be easily detected with CT. Moreover, imaging of the central nervous system, particularly by CT is essential in the differential diagnosis of syndromes with associated congenital hepatic fibrosis.

Magnetic resonance imaging (MRI), on the other hand, is an attractive alternative, especially since it does not involve the use of radiating energy. Magnetic resonance cholangiopancreatography (MRCP) allows for detailed and thorough evaluation of the biliary tree and renal abnormalities, where lesions that were missed by US may even be detected. Some authors advocate that with the advent of newer technologies like half-fourier-acquisition single-shot turbo spin-echo (HASTE) it may even be possible to quantify the extent of parenchymal fibrosis. Brain MRI is also essential to identify cerebellar malformations associated with disorders such as the Arima, Joubert and COACH syndromes (Figure 4).

Histopathological findings

A unequivocal diagnosis of congenital hepatic fibrosis can only be made by a examination of a liver biopsy. The

Figure 2 Ultrasound image of a patient with congenital hepatic fibrosis (CHF). Heterogenous appearance of hepatic parenchyma. The circled area depicts the presence of portal vein cavernous transformation.
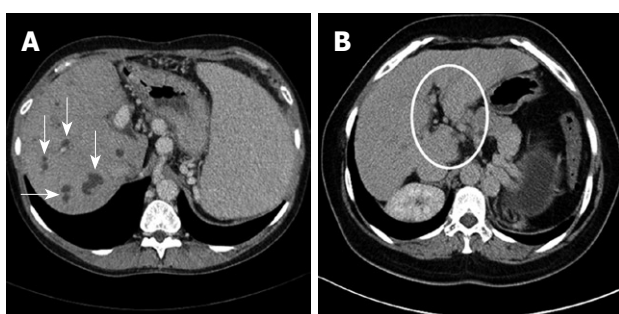

Figure 3 Abdominal computerized tomography (CT) scans of two patients with CHF. A: White arrows depict cystic dilatations of the biliary tree associated with Caroli's syndrome; B: Circled area shows portal vein cavernous transformation in a patient with Bardet-Biedl syndrome.
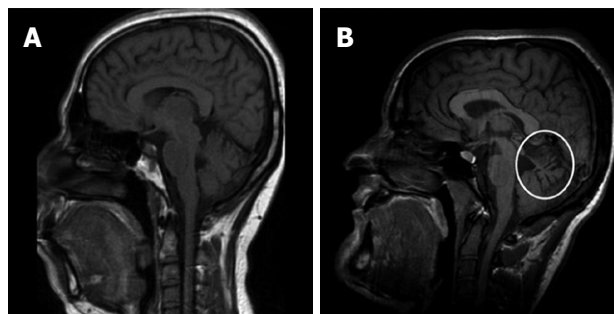

Figure 4 Brain magnetic resonance imaging (MRI) scans of two patients with congenital hepatic fibrosis. A: A patient with Bardet-Biedl syndrome with normal findings; B: The circled area depicts cerebellar vermis atrophy manifested by more prominent folds/sulci, associated with Joubert syndrome.
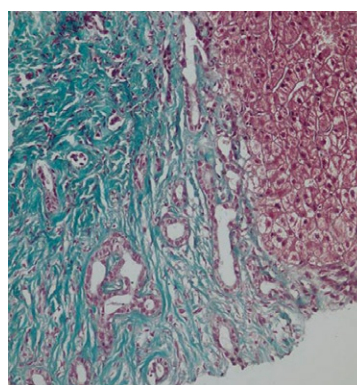

Figure 5 Liver biopsy of a patient with CHF. The left side of the image depicts a portal area with extensive fibrosis and the presence of several bile ducts with cuboidal epithelium that have arrested at different stages of the maturation process. On the right, hepatocytes with normal morphology may be seen (× 230, trichrome stain).

classical histological findings of this disorder are varying degrees of hepatic fibrosis with nodular formation, which may become extensive as the disease progresses. In the eyes of inexperienced pathologists, histopathological findings may easily be mistaken for cirrhosis. In CHF, widened fibrous bands may be encountered in the portal tract containing an increased number of irregularly shaped proliferating bile ducts lined by normal cuboidal epithelium. Unlike cirrhosis, hepatic lobules are usually normal with normal hepatocyte morphology, particularly in the early stages (Figure 5). Signs of cholestasis may be observed in the setting of associated cholangitis. Other findings include cystic dilatation of bile ducts (Caroli's disease), and hypoplasia of the portal vein branches in association with supernumerous hepatic artery branches. In fact, congenital absence of the portal vein has been reported in a pediatric patient with CHF[29]. Similarly, considering the close association of portal vein cavernous transformation with CHF, it has been postulated that such a portal vein anomaly may be a component of the disorder, rather than a consequence, since bile ducts and portal veins share embryonic origins[7].

TREATMENT

As yet, no treatment modality has been shown to actually stop or even reverse the pathological process in con-

genital hepatic fibrosis, and it remains a progressive and debilitating condition. However, extensive research has been underway into the pathogenesis of fibrosis of the liver, particularly in the setting of chronic liver diseases, and some of the treatment options available may in fact be extended to CHF patients. Instead, for CHF, treatment is directed at the management of its complications.

Anti-fibrotic therapy
Several agents have been studied, particularly in the setting of chronic liver disease. Although results have been promising, especially in animal studies, the clinical impact on humans has failed to live up to expectations. For example, colchicine is a plant alkaloid that inhibits polymerization of microtubules, and is believed to be antifibrotic, preventing collagen secretion and deposition. It had been shown to effectively inhibit collagen synthesis and fibrosis in experimental animal models, however almost all clinical trials, as well as several meta analyses, failed to show any benefits in humans, and current recommendations do not include colchicine as an antifibrotic agent[30].

The angiotensin Ⅱ system, on the other hand, represents an extremely attractive antifibrotic target, as overproduction of angiotensin Ⅱ has been shown to stimulate stellate cell activation and fibrogenesis in the liver.

Table 2 Several antifibrotic agents studied in the setting of hepatic fibrosis of different etiologies[33-43]

Authors	Antifibrotic agent studied	Patient group (*n*)	Dose used	Therapeutic efficacy
Kershenobich *et al*[33], 1988	Colchicine	Cirrhosis - all causes (100)	0.6-1.8 mg/d	5-yr survival rates: colchicine 75%, placebo 34%; Histological improvement: colchicine 30%, placebo 0%
Pockros *et al*[34], 2007	IFN-γ	Cirrhosis - HCV-related (488)	IFN-γ 1b 100 mg and 200 mg	Histological improvement in select group with IFN-inducible T cell a chemoattractant (I-TAC),
Weng *et al*[35], 2005	IFN-γ	Cirrhosis - HBV-related (99)	50 mg IFN-γ intramuscularly on a daily basis for 3 mo	Histological improvement: treatment group 63%, control group 24.1%
Debernardi-Venon *et al*[36], 2007	Angiotensin Ⅱ receptor blockers (candesartan)	Cirrhosis - all causes (47)	8 mg/d	Has been shown to decrease hepatic venous pressure gradient in patients with cirrhotic portal hypertension; studies investigating histological improvement still underway
Neuschwander-Tetri *et al*[37], 2003	PPAR ligands (rosiglitazone)	NASH associated fibrosis (30)	4-8 mg/d	Significant improvements in zone 3 perisinusoidal fibrosis
Armendáriz-Borunda *et al*[38], 2006	Pirfenidone	HCV-related fibrosis (15)	1200 mg/d	Histological improvement in 30% of patients
Ferenci *et al*[39], 1989	Silymarin	Cirrhosis - all causes (170)	140 mg three times daily	4-yr survival rate: silymarin 58%, placebo 39%; no histopathological studies available
Nelson *et al*[40], 2003	Interleukin-10	HCV related fibrosis (30)	subcutaneously at a daily or thrice weekly dose of 8 pg/kg or a thrice weekly dose of 4 pg/kg	Significant improvements in histology
Poupon *et al*[41], 2003	Ursodeoxycholic acid	PBC (367)	15-20 mg/kg per day	Significantly delayed progression of histopathological changes
Lieber *et al*[42,43], 2003	Polyenyl-phosphatidylcholine	Chronic alcoholics (789)	1.5 g three times daily	No improvement in fibrosis; new study underway

HCV: hepatitis C virus; HBV: Hepatitis B virus; IFN-γ: Interferon-γ; PPAR: Peroxisome proliferator-activated receptor; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cirrhosis.

Angiotensin Ⅱ may also play a role in the pathogenesis of portal hypertension, thus providing an added benefit to attempts inhibiting the system. The data in humans, however, has been mixed, with no conclusive evidence supporting the use of angiotensin receptor blockers for the prevention of liver fibrosis[30].

Pirfenidone, another promising antifibrotic agent, whose mechanism of action is not clearly understood, was found to be useful in the management of idiopathic pulmonary fibrosis. Its benefit on liver fibrosis has yet to be sufficiently investigated. Other potential antifibrotic agents have been listed in Table 2[30].

Endoscopic therapy
Endoscopic treatment is the mainstay for primary and secondary prophylactic management of esophageal and gastric varices, as well as in the setting of acute bleeding. Similarly, for the management of recurrent cholangitis attacks associated with Caroli's syndrome, besides the use of antibiotics, drainage and stone extraction using endoscopic retrograde cholangiopancreatography (ERCP) may be indicated.

Radiological intervention
Transjugular intrahepatic portosystemic shunts are considered for patients not amenable to sclerotherapy, and is particularly valuable in treating patients with refractory bleeding to buy time until liver transplantation.

Surgery
Surgical shunts may also be indicated with the aim of portal decompression in patients with variceal bleeding not

satisfactorily managed endoscopically. Procedures of choice include nonselective total portosystemic shunts, nonselective partial portosystemic shunts that maintain some antegrade blood flow to the liver and selective portosystemic shunts, which decompress the gastroesophageal junction and the spleen through the splenic vein to the left renal vein. On the other hand, for Caroli's disease with recurrent bouts of cholangitis, partial liver resection may be indicated in case of extensive heterogenous involvement of a segment of the liver.

Liver transplantation
Liver transplantation is the only known cure for CHF, and is indicated at the later stages of the disease, with the development of signs of liver failure. In Caroli's syndrome, frequent recurrence of cholangitis with diffuse involvement of the liver is also an indication for transplantation[9,10,31]. In 2008, Rossi *et al*[32] reported on three patients who had co-incidental hepatic failure due to CHF and end-stage renal failure as a result of polycystic kidney disease. All three underwent successful liver and kidney transplantation (1 simultaneous and 2 sequential) with excellent long term results.

HACETTEPE EXPERIENCE
Throughout the 35 years between 1974-2009 in the history of the Department of Gastroenterology at Hacettepe University, Ankara, a total of 26 patients, 16 female and 10 male, with an average age of presentation of 28.4 years, have been diagnosed with congenital hepatic fibrosis. While up to the year 1985 only 3 patients were diagnosed,

the remaining 23 patients were diagnosed in the 1990s and particularly after the year 2000. This may be attributed to better recognition of the disorder by both clinicians and pathologists.

The most common presenting symptom was abdominal distention (11/26 - 42.3%) attributed to hepatosplenomegaly, with a history of recurrent cholangitis present in 6/26 (23%) of patients. In only two patients (7.7%) bleeding from esophageal varices was the presenting finding.

In 8/26 patients (31%) CHF was found to be in association with Caroli's disease (a combination otherwise known as Caroli syndrome). Incidentally, all patients who presented with signs of cholangitis suffered from Caroli's disease, where cholangitis is an expected manifestation. Joubert's syndrome with associated cerebellar vermis anomalies was diagnosed in 2 patients. In 2008, three siblings were referred to the department with common findings including mental retardation, blurred vision, nystagmus, truncal obesity, optic fundal and neurological abnormalities. Further investigation into the possible etiology of co-incidental hepatosplenomegaly resulted in a diagnosis of CHF after liver biopsy. All three were diagnosed as suffering from Bardet Biedl syndrome.

All but three of the patients under follow-up in our department are alive and well. Two patients died after contracting cholangiocellular cancer, while the third patient with Caroli's disease who had undergone several endoscopic gall stone extraction procedures died of biliary sepsis in 2002. Three patients, all of whom had Caroli's syndrome, underwent successful liver transplantation.

CONCLUSION

CHF is a very rare disorder usually occurring in association with other fibropolycystic disorders, including renal involvement. Thus, pure/isolated CHF is very rare. It is necessary to differentiate it from idiopathic portal hypertension and early liver cirrhosis. After a diagnosis of CHF is established, the physician must investigate other organ systems, particularly for neuromuscular or renal involvement. A liver biopsy is essential in the diagnosis and differential diagnosis of CHF, as the presence of small bile duct dilatation and proliferation would rule out other metabolic disorders of the liver.

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