



## **Overview of Congenital Hepatic Fibrosis in Pediatrics: A Review**

**Ahmed AbdelSamie Fadl<sup>a,b\*#</sup>, Sarah jamal almujil<sup>c≡</sup>,  
Ahmed Saeed S. Banheem<sup>d</sup>, Nasser Naif Alsuhaime<sup>e</sup>,  
Mansour Hemaied Alhelali<sup>f</sup>, Dhiyaa Hassan A. Aldukhi<sup>g</sup>,  
Khalil Rafed B. Alsaedi<sup>f</sup>, Naif Mohammed Al-Wagdani<sup>h</sup>,  
Ebtesam Ali S. Almadi<sup>i</sup>, Khalid Mohammed A. Aladhadh<sup>j≡</sup>  
and Fahad Amrh AlAjmi<sup>k</sup>**

<sup>a</sup> Doctor Samir Abbas Hospital, Saudi Arabia.

<sup>b</sup> Department of pediatrics Alazhar University Hospitals, Cairo, Egypt.

<sup>c</sup> KAUH, Saudi Arabia.

<sup>d</sup> King Abdullah Medical Complex Jeddah, Saudi Arabia.

<sup>e</sup> Al-Rayan Colleges, Medina, Saudi Arabia.

<sup>f</sup> Medical Rehabilitation Hospital, Saudi Arabia.

<sup>g</sup> Medical Graduate, Saudi Arabia.

<sup>h</sup> King Abdulaziz Hospital, Jeddah, Saudi Arabia.

<sup>i</sup> Qassim University, Saudi Arabia.

<sup>j</sup> King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia.

<sup>k</sup> Farwaniyah Hospital, Kuwait.

### **Author's contribution**

*The sole author designed, analysed, interpreted and prepared the manuscript.*

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## **ABSTRACT**

Congenital hepatic fibrosis is a rare developmental illness caused by a ductal plate malformation, often known as ciliopathy or fibrocystic liver disease. Hepatosplenomegaly and portal hypertension are two symptoms. The disease affects 1/10000–20000 people. frequently associated with a variety

<sup>#</sup> Pediatric Senior Registrar, Lecturer of Pediatrics;

<sup>≡</sup> Intern;

\*Corresponding author: E-mail: Dr\_fadl844@yahoo.com;

of illnesses caused by genetic abnormalities, such as autosomal recessive polycystic kidney disease (ARPKD) and Caroli syndrome. There hasn't been a way to stop or reverse the progression of congenital hepatic fibrosis until now. Clinical trials of anti-fibrotic medicines such as colchicine, interferon gamma, angiotensin II receptor blockers, pirfenidone, and ursodeoxycholic acid found no significant benefit. The only known cure for CHF is liver transplantation, which is recommended when the condition has progressed to the point when symptoms of liver failure have appeared. In this article we will be making overview of the disease. It's symptoms and diagnosis, different treatment method, and we will compare some of the articles published about the disease.

**Keywords:** *Congenital hepatic fibrosis; genetic abnormalities; autosomal recessive polycystic kidney disease.*

## 1. INTRODUCTION

Congenital Hepatic Fibrosis CHF is an autosomal recessive illness that primarily affects the hepatobiliary and renal systems. Hepatic fibrosis, portal hypertension, and renal cystic disease are all symptoms. It is pathologically characterized by periportal fibrosis of varying degrees and abnormally shaped proliferating bile ducts. Caroli disease, autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD) are all fibro polycystic disorders, and congenital hepatic fibrosis is one of them (ARPKD) [1].

CHF is a rare developmental illness caused by a ductal plate malformation (DPM), often known as ciliopathy or fibrocystic liver disease. Hepatosplenomegaly and portal hypertension are two symptoms. The disease affects 1/10000–20000 people [2-5]. CHF rarely manifests as a distinct entity, but it is frequently associated with a variety of illnesses caused by genetic abnormalities, such as autosomal recessive polycystic kidney disease (ARPKD) and Caroli syndrome. Due to latent aetiology and increased awareness about congenital disease, pediatric-onset liver problems are becoming more common in adult hepatology practises [6-9].

The fundamental mechanism of CHF pathogenesis appears to be ductal plate distortion as a result of aberrant biliary system remodelling. The biliary system is formed by the ductal plate, and its failure results in an excess of embryologic bile ducts and anomalies of portal vein branches. The stage of biliary anomalies during foetal development has a big impact on the overall clinical and pathologic characteristics [10-12]. The ductal plate defect in normal CHF is at the level of the smaller interlobular bile ducts. In patients with Caroli disease, however, the bigger intrahepatic bile ducts are damaged. Many cases of Caroli illness and CHF have been

described, which can be explained by ductal plate deformity affecting various intrahepatic bile duct segments. The literature has long established links between CHF and similar ductal plate malformations such Caroli disease, Von Meyenburg complex (bile duct hamartoma), and choledochal cysts. These factors might cause heterogeneity in clinical and pathologic presentations, making diagnosis difficult. Congenital hepatic fibrosis is frequently linked to ARPKD, resulting in extra clinical consequences and a worse outcome [13].

There hasn't been a way to stop or reverse the progression of congenital hepatic fibrosis until now. Clinical trials of anti-fibrotic medicines such as colchicine, interferon gamma, angiotensin II receptor blockers, pirfenidone, and ursodeoxycholic acid found no significant benefit. Symptomatic treatment is determined on the type of CHF. It is linked to the treatment of varices and bleeding in the portal hypertensive type. Endoscopic treatment, first with sclerotherapy and now with EVL, is utilised for acute bleeding as well as primary and secondary preventive purposes [14].

## 2. PATHOPHYSIOLOGY

A deformity of the ductal plate (the embryological predecessor of the biliary system), secondary biliary strictures, and periportal fibrosis cause congenital hepatic fibrosis. The development of portal hypertension follows as a result of this. The ductal plate is a spherical layer of cells that surrounds a portal vein branch. It's a forerunner of the bile ducts that run through the liver. At a distance from the hilum, ductal plates form around the smaller portal vein branches. At 12 weeks' gestation, progressive remodelling begins. The ductal plate gives rise to both interlobular and intralobular bile ductules. The lack of ductal plate remodelling leads to the persistence of an excess of embryonic duct

structures. The ductal plate malformation is characterized by the persistence of the ductal plate in conjunction with an increase in duct components and portal fibrous tissue [1].

The hepatic stellate cell (HSC) is at the heart of the hepatic fibrotic process that occurs with liver disease, and it has also been demonstrated to have a role in the disease development in congenital hepatic fibrosis. TGF- is a powerful growth inhibitory and profibrotic cytokine that plays a critical part in the physiological process of wound healing as well as the pathophysiology of organ fibrosis, according to popular belief. TGF-expression has been found to be upregulated in a variety of fibrotic disorders. TGF-1 produced from Kupffer cells is principally responsible for initiating HSC activation [15-17]. TGF-1 promotes fibrosis by increasing the secretion of extracellular matrix proteins by fibroblasts and associated cell types, including the HSC in the liver. This results in the accumulation of fibrotic matrix in pathological settings or, in a more physiological environment, effective wound healing. MMP-9, another Kupffer cell product, similarly activates latent TGF-. TGF- has additional functions, including as immunomodulation and antiproliferative effects on epithelial cells, including hepatocytes [18].

autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene, which is made up of 86 exons that are assembled in a variety of ways to produce a variety of alternatively spliced transcripts. The majority of ARPKD and congenital hepatic fibrosis cases are genetically identical. However, more research and investigation needed to determine the specific pathophysiology of the link between congenital hepatic fibrosis and ADPKD. A hepatic lesion of ductal plate malformation of the interlobular bile ducts detected in all cases with congenital hepatic fibrosis-ARPKD; the difference in presentation is mostly age related. A progressive destructive cholangiopathy involving the juvenile bile duct architecture causes the gradual loss of bile duct profiles as well as increasing periportal fibrosis. As the liver illness advances, portal hypertension, splenomegaly, and esophageal varices arise. Congenital hepatic fibrosis is characterised by intrahepatic portal hypertension, which is produced by an intrahepatic blockage that affects the blood supply to the liver, resulting in cavernous changes of the portal vein and an

increase in portal venous pressure [1].

## 2.1 Epidemiology

CHF has an unknown incidence and frequency; however it is a rare condition. Only 200 patients with CHF had been documented in the literature by 1988. Most patients' first indications or symptoms of the condition are those associated with portal hypertension, particularly splenomegaly and varices, which are frequently accompanied by gastrointestinal bleeding. The clinical signs of CHF, on the other hand, are nonspecific, making diagnosis extremely challenging. The onset of symptoms and signs varies greatly, ranging from early childhood to the fifth or sixth decade of life, while most individuals are diagnosed around adolescence or young adulthood. CHF is a dynamic and progressive illness, based on the late onset of symptoms and their clinical progression [18].

## 2.2 Symptoms & Diagnosis

Swollen belly, firm, slightly enlarged, and strangely shaped liver, and blood vomiting (hematemesis) caused to bleeding from enlarged blood vessels (varices) under the inner lining of the esophagus, stomach, and intestines are the more noticeable signs. Cholangitis (inflammation of the bile ducts) is also a possibility. Diagnostic testing is used to identify the major symptoms of this illness. Many of the symptoms listed below are prevalent in people who have this illness:

- Portal hypertension is characterised by an increase in the pressure in the venous system, which transports blood from various organs to the liver (portal system). This high blood pressure is owing to a possible congenital anomaly of the portal vein, as well as an obstruction of the portal blood flow to the liver due to excessive connective tissue growth in the liver.
- Swollen or dilated veins in the esophagus might occur as a result of portal hypertension.
- Hepatic Fibrosis is a connective tissue that looks like fibres and extends throughout the liver.
- An enlarged kidney is referred to as nephromegaly.
- Gastrointestinal Bleeding refers to bleeding from the oesophagus, stomach, and

intestines, which can result in red blood vomit or dark black faeces.

- Polycystic Kidney Disease (PCKD) is a hereditary condition in which cysts infiltrate both kidneys. This causes the kidney to grow in size while also lowering the quantity of functioning renal tissue due to compression.
- In persons with CHF, liver function tests are frequently normal [19].

The majority of patients have no symptoms, though some may experience mild right upper quadrant pain. Upper gastrointestinal variceal bleeding can occur in patients with a predominant portal hypertensive picture. Hepatomegaly, with a focus on the left lobe, splenomegaly, and nephromegaly are all found on physical examination. The surface of the liver is mildly nodular and firm. Mild increases in liver enzymes may be discovered through a laboratory examination. Alkaline phosphatase (ALP), -glutamyl transpeptidase (GGT), and bilirubin levels may be elevated in patients with a mainly cholangitic clinical presentation. A blood count may reveal a variety of cytopenias (leukopenia, thrombocytopenia) caused by hypersplenism. Renal function tests that are abnormal are linked to severe cystic renal disease, which can develop to end-stage renal failure [18].

## 2.3 Management

### 2.3.1 Anti-fibrotic therapy

- Colchicine is a plant alkaloid that prevents collagen secretion and deposition by inhibiting microtubule polymerization. It is also thought to be antifibrotic. Colchicine has been proven to efficiently limit collagen synthesis and fibrosis in experimental animal models, but nearly all clinical studies, as well as multiple meta-analyses, failed to show any advantages in people, and current antifibrotic recommendations do not include it [18].
- Overproduction of angiotensin II has been found to drive stellate cell activation and fibrogenesis in the liver, making the angiotensin II system a particularly appealing antifibrotic target. Angiotensin II may also play a role in the aetiology of portal hypertension, making attempts to block the system more effective. In humans, however, the evidence is equivocal, and there is no compelling

evidence to support the use of angiotensin receptor blockers to prevent liver fibrosis [18].

- Pirfenidone, another promising antifibrotic drug with a poorly defined mechanism of action, has been proven to be effective in the treatment of idiopathic pulmonary fibrosis. Its effect on liver fibrosis has yet to be thoroughly studied [18].

### 2.3.2 Endoscopic therapy

For primary and secondary preventative management of esophageal and gastric varices, as well as in the case of severe bleeding, endoscopic treatment is the gold standard. Similarly, drainage and stone extraction by endoscopic retrograde cholangiopancreatography (ERCP) may be suggested for the management of recurrent cholangitis attacks associated with Caroli's syndrome, in addition to antibiotics [18].

### 2.3.3 Radiological intervention

Patients who are not amenable to sclerotherapy may benefit from transjugular intrahepatic portosystemic shunts, which are very useful in managing refractory bleeding and buying time till liver transplantation [18].

### 2.3.4 Surgery

In individuals with variceal bleeding that has not been adequately treated endoscopically, surgical shunts may be needed for portal decompression. Nonselective total portosystemic shunts, nonselective partial portosystemic shunts that maintain some antegrade blood flow to the liver, and selective portosystemic shunts that decompress the gastroesophageal junction and the spleen via the splenic vein to the left renal vein are the procedures of choice. Partial liver resection may be indicated in cases of significant heterogeneous involvement of a segment of the liver in Caroli's disease with recurring bouts of cholangitis [18].

### 2.3.5 Transplantation of the liver

The only known cure for CHF is liver transplantation, which is recommended when the condition has progressed to the point when symptoms of liver failure have appeared. In Caroli's condition, recurrent cholangitis with diffuse liver involvement is also a sign that transplantation is needed [18].

### 3. DISCUSSION

In a study, clinical features were compared between children and adults. The study included eight individuals, four children and four adults, who were all diagnosed with congenital hepatic fibrosis. The children who developed serious complications of portal hypertension and required liver transplantation ranged in age from 1 to 15 years old at the time of onset. Adults between the ages of 26 and 60 developed the illness. At the start of the illness, three adults complained of recurrent abnormal liver function, and they were mostly treated conservatively. Thirty children and 33 adults were included in the literature evaluation. Hepatomegaly was shown to be more frequent in youngsters than in adults (57 percent vs. 21 percent). Eyes, other digestive organs, and the genital and central nervous systems were all involved, as were kidney malformations and bile duct anomalies. Conclusions. Children with severe consequences of portal hypertension required liver transplantation, but adults with mild-to-moderate liver injuries frequently had mild-to-moderate liver injuries at the time of commencement. The clinical symptoms of adults with CHF vary greatly. A diagnosis is easier to determine when multiple organs are involved and the course is uncommon. For a definitive diagnosis and early intervention, timely histological examination by liver biopsy and multidisciplinary collaboration are essential [6].

Wu et al. observed 60 children with CHF, with 43 percent having portal hypertension (PF CHF), 5% having cholangitic CHF, 50% having combined portal hypertensive and cholangitic CHF, and the remaining 2% having latent CHF. They found that children with mixed CHF had higher plasma prothrombin time, serum levels of alanine and aspartate transaminase, and gammaglutamyltransferase than those with PH CHF in their study [14,20].

#### 3.1 In a Study that Investigated Etiopathogenesis of Pediatric Biliary Diseases Autosomal

Recessive polycystic kidney disease (ARPKD) with ductal plate malformation affects PCK rats and Calori's disease with CHF. In ARPKD, PKHD1 mutations have been found, and fibrocystin, a PKHD1 product found in the cilia of bile ducts, is absent in the pathologic intrahepatic bile ducts. Disordered cell kinetics, including biliary epithelial cell (BEC) apoptosis, may be linked to ductal plate malformation, and laminin and type IV collagen were

immunohistochemically reduced in the basement membrane of ARPKD intrahepatic bile ducts, suggesting that this reduction is another factor in bile duct dilatation. Non-resolving hepatic fibrosis is caused by an abundance of connective tissue growth factor maintained diffusely in heparan sulphate proteoglycan in the fibrous portal pathways. Furthermore, pathologic ARPKD BECs may develop mesenchymal characteristics and play a role in the progression of hepatic fibrosis by generating extracellular matrix molecules. An initial virus-induced, T-cell mediated autoimmune-mediated cholangiopathy has been identified in an animal model of BA. In human BA, virus-driven apoptosis of BECs by a TNF-related apoptosis-inducing ligand is also postulated, followed by progressive obliteration of bile ducts, and epithelial mesenchymal transition of BECs generated by viral infection may be involved in the fibrotic process in sclerosing cholangitis. The role of viral infections in the afflicted tissues, on the other hand, is debatable. Comprehensive and analytical research of ARPKD and BA using human and animal models may lead to a better understanding of their etiopathogenesis and the development of new therapeutic options [21].

In a Study that looked at Phenotypic Variation. At the time of clinical presentation, there were 40 children (22 boys) with a median age of 1.3 years. In the newborn era, 14 of 40 (35%) children appeared with mainly renal illness, with Caroli syndrome accounting for 11 (78%) of those. Caroli syndrome and CHF both had significant PHT with oesophageal varices, with no difference in the incidence of gastrointestinal haemorrhage and varices. Cholangitis developed in 10 of the 40 people (25%) who had the Caroli syndrome, and it was more prevalent in the Caroli syndrome group. Caroli syndrome was associated with a greater rate of chronic kidney disease (CKD) stage 3 and above than CHF (85 percent vs 42 percent). In the Caroli syndrome and CHF groups, 12 of 21 (57%) and 8 of 19 (42%) children required a combined liver-kidney or isolated liver transplant, with end-stage renal disease (CKD5d) with or without advanced PHT or cholangitis being the most common reason for renal transplantation. Before the age of 14, all 14 (100%) neonatal presentation children developed CKD5d and required a combined liver-kidney transplant, whereas 77 percent of children who presented after the neonatal period survived without a liver-kidney transplant. The strongest predictor of the need for a transplant was the neonatal presentation [22].

A study that looked at the CHF in last 20 years: It included 63 cases in China during the last 20 years, comprising 30 children (around 10 years old) and 33 adults (around 31 years old), with 88.89 percent (56/63) of them being definitively pathologically diagnosed and the rest being clinically diagnosed based on clinical manifestations and family histories. In four families, CHF was found in siblings ranging in age from 6 to 21 years old. In the same family, the onset age, disease course, and associated comorbidities were all similar. In addition, five sporadic adult patients had a family history of cirrhosis and polycystic liver and kidneys. In addition, only five patients in five case reports underwent genetic testing. Two adults with polycystic kidneys were found to have PKHD1 and PKD1 heterozygous mutations. NPHP2 and CC2D2A mutations were discovered in an 18-year-old female who had polycystic ovarian syndrome and polycystic liver disease. PKHD1 and PKD1 mutations were found in two families who got high-throughput sequencing, and Sanger sequencing proved that the compound heterozygous mutations originated from their parents. The proportion of children with hepatic hepatomegaly was substantially higher than that of adults (57 percent vs. 21 percent). There were no significant variations between the two populations in any other manifestation. Adult patients with malformations of the kidneys and bile duct anomalies account for up to 50% of all cases. Furthermore, we discovered multiorgan involvement, including the eyes, lungs, genital system, and central nervous system, prompting us to assess the likelihood of CHF [6].

Various researchers are attempting to discover a medicine that might slow or even reverse the progression of fibrosis. Colchicine, angiotensin II blocker, interferon gamma, and pirfenidone are examples of medications that have showed promise in animal research but not in people [13,23-25]. As a result, the current therapy strategy for CHF is to treat the disease's consequences. Combined kidney and liver transplantation may be required in cases of linked renal and hepatic disorders. Furthermore, one study found that patients with liver and kidney illness who received solely a liver transplant improved their renal function [13,26,27].

#### 4. CONCLUSION

Without doubt Congenital Hepatic Disorder is one of the most Serious conditions that could

face the medical systems. Luckily, it's rare disease and happens 1 in every 20 thousand patients according to studies. Children and most importantly neonates must be carefully monitored for any symptoms of the disease. Right now the cure for the disease is largely liver transplant with more of anti-fibrotic drugs under development. Unfortunately, none of these drugs has showed enough effectiveness and thus we hope for better treatment options in the future.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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