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Congenital Hepatic Fibrosis: A Case Report with Review of the Literature

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Abstract

Congenital hepatic fibrosis (CHF) is a rare genetic disease, transmitted in an autosomal recessive mode. It is due to a malformation of the ductal plate of the intrahepatic bile ducts during embryogenesis at the origin of an ectasia of these ducts with the formation of a periportal fibrosis encircling the ducts. Its incidence and exact prevalence are not known, to date a few rare cases of CHF have been reported in the literature. It can appear at any age, from infancy to the fifth or sixth decade. Its clinical presentation is very variable, ranging from asymptomatic forms to forms with severe portal hypertension. It may be isolated or associated with other ciliopathies, notably autosomal recessive polycystic kidney disease and Caroli disease, rarely juvenile nephronophthisis, autosomal dominant polycystic kidney disease and various syndromic conditions. Liver biopsy remains the gold standard for confirming the diagnosis. However, imaging data may guide us. The aim of our paper is to discuss the various clinical manifestations that should be considered as suggestive of this pathology, as well as the imaging and histological findings, given the rarity and heterogeneity of the clinical forms of this pathology. We present the case of a young patient who was admitted for digestive hemorrhage, after assessing the patient's condition and stabilization, an etiological workup was performed, including ultrasound, viral serology and autoimmunity tests, all of which came back normal, necessitating liver biopsy, which came back in favor of congenital liver fibrosis.

Subject Areas

Hepatology

Keywords

Autosomal Recessive Polycystic Kidney Disease, Ductal Plate,

Portal Hypertension

1. Introduction

Congenital hepatic fibrosis (CHF) is a rare genetic disease of autosomal recessive transmission. It is due to a malformation of the ductal plate of the interlobular bile ducts during embryogenesis, causing the more or less complete persistence of the embryological biliary structures at the origin of dystrophy of the intrahepatic bile ducts and of portal fibrosis that encircle the bile ducts. This abnormality of the ductal plate itself is secondary to a dysfunction of the cilia thus classifying them in the category of ciliopathies [1]. The diagnosis is often made in front of hepatomegaly and signs of portal hypertension, rarely in front of episodes of cholangitis, classically the lobular architecture and the hepatic function are preserved. This condition may occur in isolation, but it is often associated with Caroli disease and renal anomalies characterized by pre-calcification tubular ectasia, rarely it is associated with juvenile nephronophthisis, autosomal dominant polycystic hepatorenal disease, hamartomas and various syndromic conditions (Meckel, Bardet-Biedl, Arima, Joubert…) [2]. Given the rarity of cases reported in the literature and the diagnostic difficulty of this pathology, we present here a case of CHF diagnosed on clinical, radiological and anatomi-cal-pathological data, informed consent was obtained from the patient to report this case.

2. Clinical Observation

We report the case of a 23-year-old patient born at full term, 2nd of 5 siblings, from a second-degree consanguineous marriage without antenatal or perinatal complications. The patient is a smoker (10 packages per year) and is being followed for autosomal recessive polycystic kidney disease discovered at the age of 6 months and complicated for 2 years by chronic renal failure, under a angiotensin-converting enzyme inhibitor. He was admitted with moderate hematemesis with melenas, no abdominal pain, no jaundice, no transit disorders, no vomiting and no fever. On clinical examination, hepatomegaly with a liver arrow at 16 cm, splenomegaly at 3 fingerbreadths, and collateral venous circulation with cutaneous-mucosal pallor was noted, and there was no decline dullness or neurological signs. Biology revealed anemia at 5.6 normochromic normocytic, thrombocytopenia at 86,000, disturbance of renal function with urea at 1.38 g/l, creatinine at 20.49 mg/l and glomerular filtration rate at 42.6 ml/min. Total bilirubin, prothrombin time, transaminases, cholestatic enzymes and albumin were normal (**Table 1**). The patient was transfused with 2 packed red blood cells and put on injectable octreotide and a proton pump inhibitor. The upper GI endoscopy showed the presence of a single esophageal varicose vein grade II with red signs, ligated. Abdominal ultrasound showed a liver of homogeneous echostructure,

Table 1. Biological parameters of the patient.

Biological Parameters	Value
Hb	5.6 g/dl
MCV	75 fL
MCHC	30%
Urea	1.38 g/l
Creatinine	20.49 mg/l
GFR	42.6 ml/min/1.73m^2
AST	14 UI/l
ALT	9 UI/l
Total bilirubin	5 mg/l
Albumin	38 g/l
Prothrombin time	80%
Platelet	86,000/mm^3
GGT	50 UI/l
Alkaline phosphatase	43 UI/l

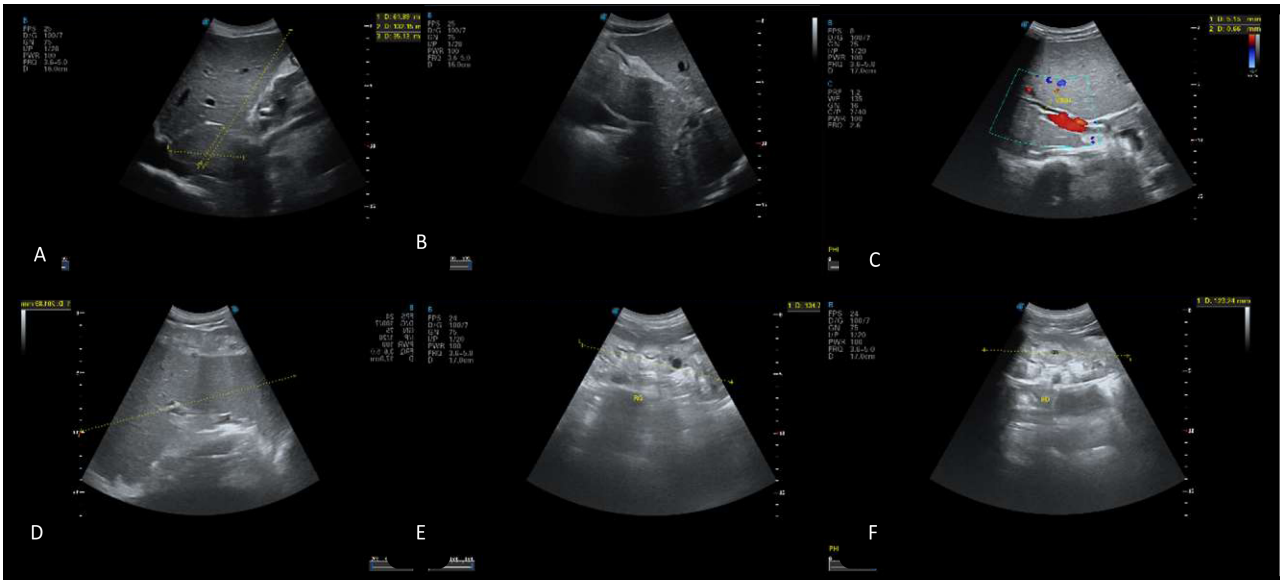

Figure 1. Ultrasound images of the patient. (A) Hypertrophy of the left liver. (B) Repermeabilization of the umbilical vein. (C) Dilated intrahepatic bile duct. (D) Splenomegaly. (E), (F) Enlarged right and left kidneys, dedifferentiated and dotted with multiple microcysts.

regular contours, dysmorphic with hypertrophy of the left liver (lateral and medial segment) without individualized focal lesions, hepatosplenomegaly, repermeabilization of the umbilical vein, a dilated portal trunk at 14.5 mm permeable and dilated intrahepatic bile ducts. The kidneys were enlarged, dedifferentiated and dotted with multiple microcysts (**Figure 1**). As part of the etiological work-up of the hepatopathy, viral serologies B and C, protide electrophoresis,

ceruloplasminemia, cupruria, hemochromatosis and metabolic work-up were performed and came back negative.

The indication for liver biopsy was given and the histopathological examination showed hepatic parenchyma cut into nodules of irregular size and shape by bands and patches of annular fibrosis, in the center of the fibrous septa there were ductal sections of greater caliber with partially dilated lumen, The fibrosis was criss-crossed by an abundant capillary or venous vascular network with few sections of portal veins and arteries, the hepatocytes were free of steatosis with no necrotic-inflammatory activity within the nodules and there was no ductal or hepatocellular cholestasis, the appearance was characteristic of congenital hepatic fibrosis (**Figure 2**). Currently, the patient is on beta-blocker for secondary prevention, with no recurrence of bleeding, no ascitic decompensation and no angiolitic complicationsat at one year follow-up. He is also followed regularly by nephrology to monitor his renal function.

3. Discussion

CHF belongs to the congenital fibrocystic liver disease. It was initially reported by Bristowe in 1856, then its varied clinical findings were described by Kerr *et al*. in 1961. Its prevalence is low and has been estimated at 1 per 100,000 births [3].

Embryologically, the epithelium of the intrahepatic bile ducts derives from the hepatic bud proper at the eighth week of gestation. This development starts in the hilar region of the liver from the hepatoblasts and progresses towards the periphery. The hepatoblasts form a cylindrical layer at this point that surrounds the future portal space and is referred to as the ductal plate. This layer of cells will secondarily duplicate forming a double biliary epithelial cylinder around the portal space. This cylinder is composed of a portal layer close to the mesenchyme and a lobular layer in continuity with the parenchyma. This temporary structure normally undergoes a remodeling that can be schematically divided into

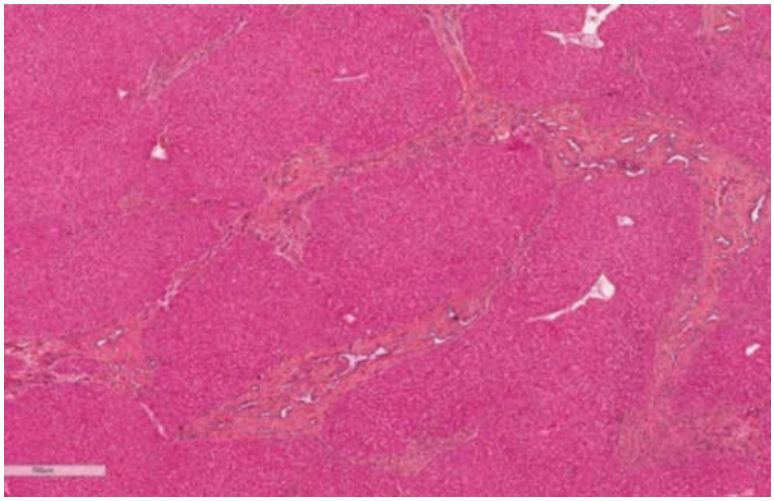

Figure 2. Typical histological appearance of CHF: Portal enlargement, intrahepatic bile ducts are ectatic and encircled by portal fibrosis.

three phases. The first phase consists in the development of peripheral tubules, these peripheral tubules will become the definitive bile ducts, during the second phase, the branches of the hepatic artery develop in the periportal mesenchyme and the third phase consists in the incorporation of the peripheral tubules inside this mesenchyme, this last phase is accompanied by a disappearance by apoptosis of the majority of the remaining structures of the ductal plate.

Cystic liver diseases are related to an embryological anomaly known as ductal plate malformation. This anomaly corresponds to a total or partial stop of the remodeling of this plate, causing the more or less complete persistence of the embryological biliary structures. Moreover, depending on the stage of maturation arrest, the diseases differ; at the level of the interlobular bile ducts, the anatomoclinic entity of CHF is produced [1]. It is characterized by the dystrophy of the intrahepatic bile ducts and portal fibrosis forming more or less wide bands that encircle the bile ducts. The anomaly of the Ductal plate itself is secondary to a dysfunction of the primary cilium caused by the mutation of the PKHD1 gene coding for a protein that is fibrocystin, expressed by the renal and biliary epithelium, this protein contributes to maintaining the three-dimensional tubular architecture, in case of genetic defect, there will be a defect in the expression of fibrocystin causing a ciliary dysfunction considered as one of the main mechanisms of cystogenesis.

Although CHF can occur in isolation, it is often associated with other ciliopathies, and the phenotype can involve multiple organs including the kidney and central nervous system. It is frequently accompanied by renal abnormalities characterized by pre-calcification tubular ectasias (Cacchi ricci disease), which are found in about two-thirds of patients. In some patients, these tubular ectasias lose communication with the rest of the urinary tract and develop into large cysts that are part of autosomal recessive polycystic kidney disease. Some authors believe that polycystic kidney disease and HCF represent a single disorder with a broad spectrum of manifestations, while others maintain that they are two distinct disorders with similar liver and biliary lesions [4] [5]. The association with Caroli's disease is also frequent and is referred to as Caroli's syndrome, as opposed to juvenile nephronophthisis, and the various syndromic conditions (Meckel, Bardet-Biedl, Arima, Joubert…) that present with less frequency; And Depending on the associated diseases, patients will present with signs and symptoms related to other organs [6] (**Table 2**). These entities can lead to heterogeneity in clinical and pathological manifestations which makes diagnosis difficult. When CHF is isolated, its clinical presentation is highly variable, ranging from completely asymptomatic forms to severe portal hypertension. The disease can occur at any age, from infancy to the fifth or sixth decade.

Four clinical forms have been defined: the form with portal hypertension, which is the most frequent and the most severe; the cholangitic form, the mixed form and the latent form. The first episode of nasogastric varicose vein rupture usually occurs between 5 and 20 years of age, which is consistent with our patient's age, but sometimes later. There is no hepatocellular insufficiency and

Table 2. Syndromes with associated congenital hepatic fibrosis.

Associated Disorders	Clinical Manifestations
Caroli syndrome	portal hypertension, Angiocholitis (pain, fever, jaundice), liver abscess, intrahepatic calculus, cholangiocarcinoma (abdominal pain, jaundice, hepatomegaly), kidney abnormalities
Autosomal dominant polycystic kidney disease	Adult, hypertension, renal cysts, chronic renal failure, often asymptomatic hepatic cysts, hepatomegaly, digestive disorders, respiratory disorders or undernutrition, jaundice and portal hypertension, cerebral aneurysms
Autosomal recessive polycystic kidney disease	Child, neonatal respiratory failure, hyponatremia, hypertension, urinary tract infection, chronic end-stage renal disease
Nephronophthisis	Polyuro-polydipsia syndrome, persistent nocturnal enuresis, chronic renal failure
von Meyenburg complexes	Often asymptomatic, incidental to liver biopsy
COACH syndrome	Hypo/aplasia of the cerebellar vermis, oligophrenia, ataxia, coloboma
Senior Loken syndrome	Nephronophthisis, retinal dystrophy, hearing loss
Bardet-Biedl syndrome	Retinitis pigmentosa Polydactyly, obesity, hypogonadism
Arima syndrome	Hypoplasia of the cerebellar vermis, retinopathy, renal cyst, psychomotor delay, nystagmus, dysmorphic face
Meckel syndrome	Microcephaly, cystic kidney disease, hypoplastic genitalia, polydactyly, biliary tract dysplasia, liver cysts
Joubert syndrome	Hypoplasia of the cerebellar vermis; retinitis pigmentosa, nystagmus

therefore bleeding is generally well tolerated. Portal hypertension may progress and lead to ascites or encephalopathy in the more advanced stages. Physical examination reveals constant and firm splenomegaly and hepatomegaly, predominantly on the left lobe, with an abdominal porta-cava. These patients classically do not present cirrhosis, they retain a hepatic lobular architecture and normal liver function. More rarely, they may present episodes of cholangitis [7]. Liver biological tests are usually normal as in our patient, they may reveal a slight elevation of liver enzymes, Patients with a predominantly cholangitis clinical picture may present with elevations of alkaline phosphatases, gamma-glutamyl transferase and bilirubin, Abnormal renal function tests are associated with extensive cystic kidney disease, which may even progress to end-stage [8]. Radiologically, ultrasound is often used as a first line because of its availability, it shows hypertrophy of the left lateral segment and the caudate lobe, a normal or

hypertrophic left medial segment, hypertrophy of the right medial lobe segment, hepatosplenomegaly, dilatation of intrahepatic and extrahepatic bile ducts with concomitant focal cystic or solid lesions and periportal thickening, stones in the bile ducts in case of associated Caroli disease, hepatic and renal cysts and cavernous transformation of the portal vein. CT has an advantage over ultrasound and allows for better representation of gross morphology of the liver with accurate volume measurements and imaging of the vasculature, as well as any changes in the biliary tree. The periportal cuffs indicative of the fibrotic process, can also be easily detected. In addition, imaging of the central nervous system, including CT, is essential in the differential diagnosis of syndromes with which CHF is associated. Magnetic resonance cholangiopancreatography allows a detailed and thorough evaluation of the biliary tree and renal abnormalities, and allows the detection of lesions that were not detected by ultrasound, we find the stigmata of hepatic fibrosis, unlike fibrosis of other origins, this one is usually accompanied by an enlargement of the medial segment of the right lobe. This fibrosis can be visualized on MRI as hypersignal trabeculae on T2-weighted sequences. Signs of complications such as portal hypertension (varicose veins, splenomegaly), and degeneration (hepatocellular carcinoma, cholangiocarcinoma) are also sought. Hepatic histology is the reference examination to confirm CHF. The histological findings are variable degrees of hepatic fibrosis with nodule formation that may become extensive as the disease progresses. There is an enlargement of the portal spaces by fibrous tissue with the presence of numerous bile ducts, more or less dilated within the portal spaces. The hepatic lobules are generally normal with a normal morphology of the hepatocytes contrary to cirrhosis where the normal lobular architecture is destroyed. Finally, the portal venules may appear hypoplastic [9]. In fact, congenital absence of the portal vein has been reported in a pediatric patient with HCF [10]. These histology findings were observed in the liver biopsy of our patient which confirmed the diagnosis. Genetic tools have a limited role in diagnosis due to the lack of sequencing panels and genetic databases covering the genes related to this condition [9]. For treatment, several antifibrotic agents (colchicine, pirfenidone, angiotensin receptor blockers, IFN gamma…) have been studied in chronic liver diseases and can actually be extended to HCF patients, Although the results are promising, especially in animal studies, the clinical impact on humans has not lived up to expectations [8]. Therefore, the therapeutic strategy for CHF, so far, is focused on the management of its complications which are angiocholitis and portal hypertension. In case of portal hypertension, the treatment can be medical based on vasoactive drugs, beta-blockers in primary or secondary prevention and diuretics, endoscopic by ligation of esophageal varices or by injection of tissue adhesive; TIPS is used in cases of refractory hemorrhage or early recurrence of hemorrhage, in cases of failure of well-conducted secondary prevention by drug and endoscopic treatment and in cases of refractory ascites. The treatment of angiocholitis is based on antibiotic therapy, in addition, the extraction of stones by endoscopic retrograde cholangio-pancreatography can be indicated for the

management of recurrent attacks of cholangitis associated with Caroli disease, surgery is reserved in the latter to symptomatic forms that have resisted conservative treatments, this is the case of severe infections and/or recurrent on a localized form where a partial hepatectomy will be proposed. When complications of portal hypertension are not controlled by conservative treatment, or in case of severe infections (angiocholitis, abscesses, sepsis) and/or recurrent infections occurring on a diffuse bilobar involvement not allowing hepatectomy; liver transplantation is required [11]. In case of associated diseases, in particular polycystic kidney disease causing end-stage renal failure, a fortiori at the dialysis stage, a combined liver/kidney transplantation should be considered [12]. However, one study showed that in patients with liver disease and kidney disease who underwent liver transplantation only, kidney function improved [13].

4. Conclusions

Congenital liver fibrosis (CHF) is a rare autosomal recessive congenital disease that usually occurs in association with other disorders mainly autosomal recessive polycystic kidney disease and Caroli disease. The isolated form is still very rare. The clinical presentation is atypical and heterogeneous in association with other ciliopathies. Therefore, when faced with unexplained portal hypertension, it is interesting to think about this rare entity and to make a liver biopsy to confirm it. The prognosis is generally good due to the preserved liver function and the absence of hepato-cellular failure, in case of association with other disorders the main cause of morbidity and mortality is the involvement of other organ systems, especially the kidneys and the central nervous system.

Congenital liver fibrosis (CHF) is a rare autosomal recessive congenital disease that usually occurs in association with other disorders. The isolated form is still very rare.

Therefore, when faced with unexplained portal hypertension, it is interesting to think about this rare entity and to make a liver biopsy to confirm it.

Conflicts of Interest

The authors declare no conflicts of interest.

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