

A family of congenital hepatic fibrosis and atypical retinitis pigmentosa

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Abstract

Congenital hepatic fibrosis is a rare cause of portal hypertension and esophageal varices in children. We report cases of siblings with biopsy proven congenital hepatic fibrosis and with atypical retinitis pigmentosa. They presented with repeated episodes of jaundice along with progressive decrease of vision in night. They had hepatosplenomegaly and portal hypertension with esophageal varices. One of the siblings had a large regenerating nodule replacing the entire right lobe of the liver and other one developed repeated hematemesis. This constellation of diagnosis belongs to the ciliopathy group of disorders. The spectrum of ciliopathy disorders has been evolving, and it varies from mild to severe manifestations.

Introduction

Congenital hepatic fibrosis (CHF) is rare cause of familial liver disease. It is a ductal plate malformation disorder and is inherited in an autosomal recessive pattern. The most common clinical presentation is portal hypertension and esophageal varices. It is associated with cystic diseases of kidney and liver and is also a part of various syndromes. We present a case of congenital hepatic fibrosis in 3 siblings of a family who also had retinal lesions; written informed consent of the parents was taken.

Case Reports

Case #1

A 12-year old male child third by birth order of four siblings and born of a third degree consanguineous marriage presented with insidious onset progressive upper abdominal fullness and episodic non-cholestatic jaundice since last 4 years. He also complained of

reduced vision at night and in dim light, epistaxis and easy bruising. There was no history of gastrointestinal bleeding or abdominal distension. He was doing well in school and there was no history of seizure. He was evaluated 3 years back in another city for deranged liver enzymes and underwent a liver biopsy. The patient then lost to follow up. The parents and eldest sister had no complaints. The weight, height and body mass index was 30 kg, 135 cm, 16.5 kg/m² (below 25th percentile), respectively. On examination he had pallor, grade 3 clubbing and hepatosplenomegaly. There was no Kayser Fleischer (KF) ring or ascites. On investigations he had elevation of transaminases more than 3 times of upper limit of normal. He also had anemia and reversal of albumin to globulin ratio. Serum creatinine was normal.

Upper gastrointestinal endoscopy showed small esophageal varices. The HBsAg and anti-hepatitis C virus antibodies were absent. The thyroid profile and lactate were normal. Urine routine and microscopic examination was normal and no reducing substances were found in the urine. Fundoscopy revealed atypical retinitis pigmentosa (Figure 1). Autoimmune markers and KF ring were absent and serum ceruloplasmin and α -fetoprotein was normal.

The ultrasonography of abdomen with Doppler was suggestive of hepatosplenomegaly with portal hypertension. The kidneys were normal. There was 8.5×7.7 cm-sized iso- to hypo-echoic well-defined lesion replacing the entire right lobe of liver. This was confirmed on magnetic resonance imaging, which revealed a large regenerating nodule, and an enlarged left lobe (Figure 2).

The liver biopsy slide, which was done three years back, were collected from previous hospital and reviewed. It was showing altered architecture of liver due to presence of nodules of varying sizes. Hepatocytes showed severe hydropic changes. The portal tracts showed lymphocytes, plasma cells, eosinophil and proliferating bile ducts with bands of fibrosis surrounding the portal tracts suggestive of congenital hepatic fibrosis (Figure 3). The patient was registered for liver transplantation. He was also advised endoscopy and hepatocellular carcinoma surveillance every 6 months.

Case #2

The younger brother aged 10 years also had similar complaints but were present since last 2 years. The weight, height and body mass index of younger brother were 25 kg, 130 cm and 14.5 kg/m² (below 5th percentile) respectively. On examination he had pallor, grade 3 clubbing and hepatosplenomegaly. There was no KF ring or ascites.

He had small esophageal varices on upper gastrointestinal endoscopy. He had hepatosplenomegaly with portal hypertension

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on ultrasonography. There were no cysts in kidneys. Rest of the laboratory evaluation was identical to elder brother. The fundoscopy revealed atypical retinitis pigmentosa. The liver biopsy was done. The findings were consistent with that of elder brother. He was started on β -blocker. He was advised surveillance as his elder brother.

Case #3

The second sister had similar complaints started at the age of 6 years. She started developing repeated episodes of hematemesis and blood transfusions 3 years later. She underwent an upper gastrointestinal endoscopy with variceal banding. She also developed ascites and underwent repeated tappings for same. She succumbed to the illness within 12 months of ascites at age of 10 years. The record of her illness was not available for analysis. Although we did not had access to her reports, the similarity of chronology of symptoms of three siblings and onset within first decade of life point towards the same etiology. The disorder must have been autosomal recessive. This was a family with rare constellation of disorders of congenital hepatic fibrosis,

retinitis pigmentosa suggesting the presence of ciliopathy. Our patients do not fit into any of the known syndromic diagnoses in literature about ciliopathies. This can be well explained by ubiquitous presence and functions of ciliary proteins in almost every major organ and the variable penetrance of the disorder.

Discussion

Congenital hepatic fibrosis is an autosomal recessive disorder, which affects liver and kidneys predominantly. It is one of the fibrocystic diseases along with caroli disease, polycystic kidney disease, choledochal cyst and von meyenburg complex. This occurs due to mutation of the ciliary proteins and they are termed as ciliopathies.¹ The ductal plate starts remodeling around portal vein and forms biliary ductules in embryo. The lack of remodeling leads to progressive fibrosis around portal vein and its branches leading to development of portal hypertension.² The mutation in ciliary proteins can also be seen in other organs such as eye and brain. These organs involvement have characteristic manifestations. The disease manifests mostly in childhood but cases were reported even in adults.³ The prevalence of congenital hepatic fibrosis in portal hypertensive children in a study from north India was 3% and most common presentation was gastrointestinal bleeding.⁴ Our patients presented with abdominal pain and decreased vision in night. These patients commonly present with failure to thrive, hematemesis, splenomegaly and fever. It has 4 types of clinical presentations in the form of portal hypertension, cholangitis, mixed, and the latent. Amongst these portal hypertension is the most common. The disease course may become complicated with cholangitis, ascites, hepatocellular carcinoma and rarely cholangiocarcinoma. CHF is generally associated with renal involvement but in our cases fortunately it was not. All 3 patients presented with night blindness and 2 of them were documented to have retinitis pigmentosa. The elder female sibling had expired so we could not confirm the findings although she also had similar symptoms. The diagnostic gold standard is liver biopsy. Our 12 year old male patient had space occupying lesion replacing entire right lobe of liver was picked up on Doppler and further characterization on magnetic resonance (MR) revealed it to be a large regenerating nodule. A liver biopsy would have been best to confirm it but with the help of dynamic MR imaging the nature of lesion could be confidently characterized.

The above findings belong to group of rare disorders, ciliopathies. As the spectrum of ciliopathies is being gradually discovered, this may be newer variant with a less drastic man-

ifestation than other well-known syndromes like Joubert syndrome. Joubert syndrome is constellation of congenital hepatic fibrosis, atypical retinitis pigmentosa, hypotonia, ataxia, nystagmus, and nephronophthisis.⁵ These patients presents early in life within the first few months to years.⁶ It will be interesting to monitor these patients for development of any neurological manifestations in future.

Nonetheless, management does not differ. The patient's management is with endoscopic and medical treatment of the varices and of intercurrent cholangitis if develops. The shunt surgeries for portal hypertension and liver transplantation can be performed in case of severe portal hypertension with refractory variceal bleeding and advanced hepatic disease respectively.⁷ These patients need period-

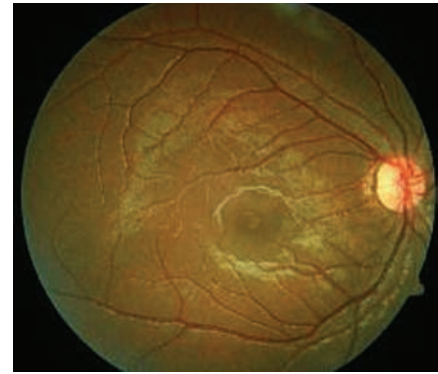


Figure 1. Hypopigmentary changes seen at posterior pole with well-circumscribed lesion at fovea. Optic disc is normal with no arteriovenous changes.

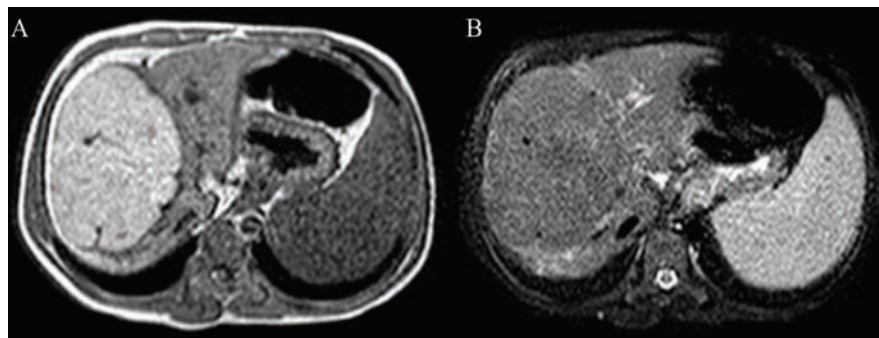


Figure 2. Magnetic resonance image showing 8.5×7.7 cm regenerating nodule in right lobe of liver without any heterogeneous intensity within it. A) T1 hyper-intense; B) T2 hypo-intense.

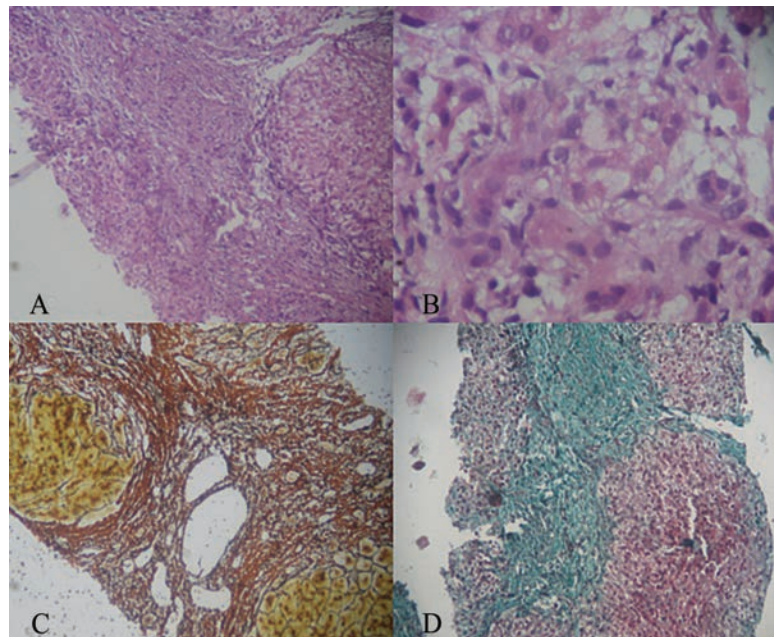


Figure 3. A) Hepatocytes are seen arranged in nodules separated by fibrous tissue. Lobular architecture is preserved. No regenerating nodules are seen [hematoxylin and eosin (H&E), 40X]; B) Hepatocytes shows hydropic changes and portal tracts showed lymphocytes, plasma cells, eosinophils with proliferating bile ducts (H&E stain, 400X); C) Presence of nodules of varying sizes on reticulin stain (40X); D) Nodules with fibrous bands surrounding portal tract on Masson's trichrome stain (40X).

ic surveillance for hepatocellular carcinoma and screening for involvement of other systems subsequently. The majority of these patients succumb due to associated renal disease. Hence prognosis depends upon other systems involved.

Conclusions

Ciliopathies are an evolving group of disorders with multisystem involvement seen due to the presence of mutations in ciliary proteins. The manifestations are variable depending upon the penetrance of the disorder. This family presented with congenital hepatic fibrosis, atypical retinitis pigmentosa. In cases of CHF

search for involvement of other system at presentation and even follow up is mandatory.

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