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Caroli's Disease vs Caroli Syndrome: Clinical and Radiological Spectrum, with disease Outcome at a Teaching Hospital in Lahore

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ABSTRACT

Background: Caroli disease and Caroli syndrome are part of the clinical spectrum of ductal plate (DP) malformations, also referred to, as the fibrocystic liver diseases. This article aimed to study both these conditions, in terms of clinical features and disease outcome at a teaching hospital. **Objective:** To describe the clinical spectrum, laboratory and imaging findings, management course and outcome of fibrocystic liver diseases in children, at the University of Child Health Sciences, Lahore, Pakistan. **Study Design:** Cross-sectional Study. **Settings:** Department of Pediatric Gastroenterology & Hepatology, University of Child Health Sciences, Lahore Pakistan. **Duration:** January 2014 to July 2017. **Methods:** The study included patients with Caroli disease and Caroli Syndrome, confirmed on the basis of characteristic findings on magnetic resonance cholangiopancreatography. SPSS v.20 was used for statistical analysis. **Results:** The mean age of 15 patients included in the study was 6.54 ± 4.18 years. Among them, 7/15 (46.7%) had Caroli's disease (CD), whereas 8/15 (53.3%) had Caroli's syndrome (CS). Male to female ratio was 4:1. CS pre-dominantly affected male children (8:0), while CD affected both genders almost equally (4:3). CD commonly presented with recurrent cholangitis (6/7, 85%), while CS as portal hypertension (7/8, 87.5%). Renal involvement was found in 5/15(33.33%) patients; mostly in CS (4/5,80%) and one (6.66%) patient progressed to end stage renal disease. One patient of CD underwent lobectomy and one died of end stage liver disease. Two patients of CS were treated with shunt surgery with partial splenectomy. Six patients are doing well after endoscopic variceal band ligation and propranolol prophylaxis. **Conclusion:** Caroli disease and Caroli syndrome are two sides of the same coin; it is important to differentiate the two disorders, especially from management point of view. CS is more common in our set up, leading to portal hypertension, which can be treated with sclerotherapy, endoscopic band ligation or shunt surgery. CD leads to cholangitis, which is managed with antibiotics.

Keywords: *Caroli's disease, Caroli syndrome, Portal hypertension, Ductal plate malformations, Fibrocystic liver disease.*

INTRODUCTION

Caroli disease and Caroli syndrome are a part of the clinical spectrum of ductal plate (DP) malformations. There is dilatation of the larger intrahepatic ducts (>50mm) in Caroli's disease. In Caroli syndrome there is malformation of interlobular and septal bile ducts (20-50mm) along with congenital hepatic fibrosis. Latter being more common than former.[1]

The first case was reported in 1818 by Todd. Later on, in 1958, Jaques Caroli described the disease in true sense and classified it into different types. It corresponds to type V choledochal cyst according to the Todani classification.[2] It's true incidence is not known; an estimate is around 1:100,000. The incidence of ARPKD and congenital hepatic fibrosis is around 1:20,000 live births.[3]

It is an autosomal recessive disease. The pathophysiologic basis of intrahepatic dilatation is abnormal remodeling of the ductal plate, with an imbalance between cellular proliferation and apoptosis.[4] In Caroli syndrome, the defect in ductal plate malformation (DPM) occurs at the level of the smaller portal tracts (20-50mm) and is associated with hepatic parenchymal fibrosis. Caroli syndrome, like Congenital Hepatic Fibrosis, has

association with autosomal recessive polycystic kidney disease (ARPKD).[5]

Caroli disease has been described as either localized or diffuse. Symptomatic Caroli's disease presents with recurrent episodes of cholangitis; which are characterized by right upper quadrant abdominal pain, along with pruritus and jaundice. The recurrent episodes of cholangitis may be complicated by intrahepatic calculi and hepatic abscess formation.[6] In Caroli's syndrome the clinical presentation is with upper GI bleed, caused by portal hypertension. Recurrent bacterial cholangitis can also be seen which can lead to chronic liver disease.[7]

Ultrasonography (USG) is a sensitive, non-invasive and readily available initial imaging modality. It demonstrates irregular dilatation of the intrahepatic as well as extrahepatic bile ducts. Cholelithiasis can be appreciated via ultrasonography. It is quite sensitive for renal evaluation regarding polycystic kidney disease as well.[8] Magnetic resonance cholangiopancreaticography (MRCP) is the best imaging modality with high sensitivity, specificity & less invasiveness. It is very useful to assess the extent as well as severity of the disease. Caroli syndrome is basically managed for its portal hypertension, either with endoscopic variceal band ligation (EVL) or shunt surgery. Recurrent cholangitis in both is managed with broad spectrum antibiotics with good gram negative and anaerobic cover.[9] Aim of our research was to study the sides of the same coin i.e., Caroli's disease and Caroli syndrome in terms of clinical presentation, management and outcome.

METHODS

This study was done at the department of Pediatric Gastroenterology & Hepatology, University of Child Health Sciences, Lahore. All patients diagnosed with Caroli's disease and Caroli syndrome, from January 2014 to July 2017, were enrolled in the study. Caroli disease was defined as presence of dilated intrahepatic biliary channels with central dot sign on computed tomography (CT) scan. Caroli syndrome (CS) was defined as Caroli's disease (CD) with presence of hepatic fibrosis on multiphasic magnetic resonance cholangiopancreatography. Renal involvement was defined as presence of enlarged kidneys with cystic changes on CT scan. End stage liver disease was defined as Child-Pugh score C; while end stage kidney disease was defined as deranged renal functions tests, in range of stage V CKD, and in consultation with a pediatric nephrologist. Portal hypertension was defined as blood flow in portal vein with less than 7cm/sec, or presence of splenic hilar varices; and esophageal varices on doppler ultrasonography, confirmed via esophagogastroduodenoscopy. We excluded all the children with chronic liver disease having diagnosis of Wilson disease, autoimmune hepatitis, vascular abnormality, or genetic cholestasis. Demographic data including age, gender, family history, consanguinity; and presenting symptoms like hematemesis, melena, pain abdomen, jaundice and fever were noted. Detailed liver function tests and renal functions tests were studied. Upper GI endoscopy was done in all patients for the evidence of esophageal or gastric varices. SSPS version 22 was used for statistical analysis. Frequency and percentages were computed for quantitative and qualitative variables.

RESULTS

A total number of 15 children were enrolled in the study, who were found to have Caroli's disease and Caroli syndrome. Mean age of diagnosis was 6.54 ± 4.18 years; and youngest among them were two children, each one of age 2.5 months. The first baby girl presented with abdominal distension and was found to have Caroli's disease with bilateral cystic disease of kidneys. Her liver function tests, and renal functions tests were absolutely normal. Second baby boy presented as sepsis and his work up revealed Caroli's disease with multiple liver abscesses. Both of them were given supportive management and currently doing well. Table 1

Table 1: Clinical profile of patients with Caroli Disease & Caroli Syndrome (n=15)

Gender	**N (%)**	**CD (N=7)**	**CS (N=8)**
Male	12 (80%)	4 (57%)	8 (100%)
Female	3 (20%)	3 (43%)	0 (0%)
Male: Female Ratio	4:1	4:3	8:0
Family history	5	3 (43%)	2 (25%)
Consanguinity	15	7 (100%)	8 (100%)
Types		**N (%)**	
Caroli's Disease (CD)		7 (46.7%)	
Caroli Syndrome (CS)		8 (53.3%)	
Caroli's Disease + Kidney involvement		1 (6.66%)	
Caroli Syndrome + Kidney involvement		4 (26.66%)	
CD: CS Ratio		1:14	
Kidney involvement - CD: CS Ratio		1:4	
Clinical Presentation	**N (%)**	**CD (N=7)**	**CS (N=8)**
Pain Epigastrium/RHC	12 (80%)	6 (85.7%)	6 (75%)
Fever	14 (93.3%)	7 (100%)	7 (87.5%)
Jaundice	4 (26.4%)	4 (57%)	0 (0%)
Ascites	2 (13.3%)	2 (28.5%)	0 (0%)
Chronic Liver Disease	1 (6.7%)	1 (14.3 %)	0 (0%)
Hematemesis	8 (53.3%)	1 (14.3 %)	7 (87.5%)
Portal Hypertension	9 (53.3%)	1 (14.3 %)	8 (100%)
Chronic Kidney Disease	1 (6.7%)	0 (0%)	1 (12.5%)
Renal involvement	5 (33.33%)	1 (14.3 %)	4 (50%)
Disease Distribution	**N (%)**	**CD (N=7)**	**CS (N=8)**
Segmental disease	2 (13.3%)	2 (28.5%)	0 (0%)
Diffuse liver involvement	13 (86.66%)	5 (71.4%)	8 (100%)

**N=Number of patients, CD= Caroli Disease, CS=Caroli Syndrome, n=Total number of cases, %=Percentage*

All suspected cases of Caroli's disease on ultrasonography (USG) were confirmed by magnetic resonance cholangiopancreatography (MRCP). All patients with CS (8/8) and one patient with CD (1/8) had portal hypertension, which was confirmed both via doppler ultrasonography findings and esophago-gastro duodenoscopy (Table I). Endoscopic variceal band ligation (EVL) was performed in all nine cases with portal hypertension (both CD and CS). The minimum age of presentation with portal hypertension was 3.9 years.

Renal involvement was found in 5(33.3%) patients; most of them were with CD (4/5) as compared to CS (1/5). The child with CS had autosomal recessive polycystic kidney disease while children with CD had medullary sponge kidney disease (Table 2). Only one out of five children with renal involvement progressed to chronic kidney disease stage V, after 8 years of diagnosis (at 11 years of age). He is currently on hemodialysis. Rest of the patients with renal involvement (4/5) have normal renal functions tests.

Table 2: Complications & associations in patients with Caroli Disease & Caroli Syndrome (n=15)

Complications & Associations	Caroli's Disease (CD) N=7	Caroli's Syndrome (CS) N=8
Renal Involvement	1 (14.3%)	4 (50%)
Portal Hypertension	1 (14.3%)	7 (86%)
Cholangitis	6 (87%)	1(12.5%)
Liver Abscesses	1 (14.3%)	0 (0%)
Chronic Liver Disease	2 (28.5%)	2 (25%)
Chronic Kidney Disease	0 (0%)	1 (12.5%)
Cholangiocarcinoma	0 (0%)	0 (0%)
Choledocholithiasis	0 (0%)	0 (0%)
Outcome		
Death	1 (14.3%)	0 (0%)
Liver Transplant	0 (0%)	1 (12.5%)
Shunt Surgery	0 (0%)	2 (25%)
Endoscopy Band Ligation	1(14.3%)	8 (100%)

**N=Number of patients, CD= Caroli Disease, CS=Caroli Syndrome, n=Total number of cases, %=Percentage*

DISCUSSION

Fibrocystic liver diseases are rare genetic disorders of ductal plate malformation, and till date 200 plus cases have been reported in the literature. Caroli's disease and Caroli's syndrome represent spectrum of the same disorder; which depends on the level of anatomical insult during embryogenesis. In literature, more cases of Caroli Syndrome have been reported, as compared to those of Caroli Disease.[10] This fact is confirmed in our study in which the incidence of CS was more as compared to CD.

Caroli syndrome represents a condition which has features of both Caroli disease and congenital hepatic fibrosis. CD can present early or later in life; disease manifestation is in the form of recurrent cholangitis; with fever, pain right hypochondrium and jaundice (Charcot's Triad), as we have found in our study.[11] The recurrent cholangitis is responsible for progression to chronic liver disease. Cholangitis either causes cholestasis and parenchymal damage, or cholelithiasis and obstructive jaundice causing biliary cirrhosis. Recurrent cholangitis can also lead to portal vein thrombosis and cavernous transformation as described in literature.[12] One of our cases with CS presented with cholangitis. Two cases developed chronic liver disease; one of them needed liver transplant at 12 years of age. These patients can have abdominal pain due to pancreatitis, cholelithiasis and choledocholithiasis. However, none of our cases had choledocholithiasis or cholangiocarcinoma. Liver abscess is also rare, but a possible disease complication. One of our patients with cholangitis developed liver abscess as a complication. Children with CS mainly presented with portal hypertension, and age of presentation was late as compared to CD; no case with CS presented in infancy. The minimum age of portal hypertension was 3.5 years which is earlier than that described in literature.[13] This patient had enlarged spleen, but no complaint of upper GI bleed; and was found to have esophageal varices on surveillance esophago-gastroduodenoscopy.

The laboratory findings are neither helpful in diagnosing Caroli's disease, nor differentiate it from Caroli syndrome, same we found in this case series. Serum transaminase levels become raised, with elevated total leucocyte cell count or erythrocyte sedimentation rate during cholangitis. In our study, we found ultrasonography as the best radiological modality for screening for Caroli's disease. This is cheap, noninvasive and radiation free. Gorka *et al* also recommended ultrasonography studies for diagnosis of Caroli's disease.[14] Gadolinium enhanced MR imaging is a non-invasive technique which helps to confirm the diagnosis by visualizing the central dot sign. MR imaging is also helpful in detecting accompanying complications such as portal hypertension, hepatic and kidney disease.[15]

Kidney involvement in Caroli's disease manifests as dilatation of the collecting ducts, renal cortical cysts, autosomal recessive polycystic kidney disease and medullary sponge kidney.[15] In our study five children had renal involvement, four of them had medullary sponge kidney and one had polycystic kidney, as identified by the imaging findings. One child progressed to develop stage V chronic kidney disease, currently on hemodialysis. Caroli's disease may progress to cholangiocarcinoma, however this disease complication is more common in adolescents and adults.[16] None of our patients have developed such malignancy so far.

In Caroli syndrome (CS), the main complication is portal hypertension. Acute variceal hemorrhage is managed with vasopressin or somatostatin analogues, and early

endoscopic sclerotherapy and band ligation.[17] All our cases were managed on the same lines. Portocaval shunt, with or without partial splenectomy, is performed when sclerotherapy or banding ligation (EVL) is not effective; and patients develop complication of hypersplenism. Two of our patients got shunt surgery, because of complications of portal hypertension.

If one lobe of liver is involved, lobectomy completely relieves the symptoms. In diffuse involvement of both lobes of liver, surgical procedures like choledocho-jejunostomy and Roux-en-Y hepaticojejunostomy are performed.[18] Liver transplantation (OLT) is the only definitive treatment for symptomatic Caroli's disease and Caroli syndrome. Indications for OLT include recurrent cholangitis and/or early malignant transformation of the biliary tract.[19] In case of associated renal disease, combined kidney and liver transplant is preferred, with the timing depending mostly on need for renal transplant.

CONCLUSION

Caroli disease and Caroli syndrome are two sides of a coin; it is important to differentiate the two disorders; to identify the complications, and from management point of view. Fibrocystic liver diseases contribute significantly to disease burden with portal hypertension. CS is more common in our set up, leading to portal hypertension, which can be treated with sclerotherapy, endoscopic band ligation or shunt surgery. CD leads to cholangitis, which is managed with antibiotics.

LIMITATIONS

The limitation of this study included lack of liver biopsy findings, as it is an invasive procedure and was refused by almost all the parents. However, keeping in mind the diagnostic accuracy of magnetic resonance imaging, it was preferred for confirmation of both Caroli disease and Caroli syndrome. Furthermore, liver biopsy did not seem to help in deciding the course for disease management, therefore it was omitted.

SUGGESTIONS / RECOMMENDATIONS

We recommend that fibrocystic diseases are a rare group of disorders in children; therefore, further research should be conducted regarding these disorders in our population. So that we can generate more data and literature regarding the disease spectrum and outcome, in this part of the world.

CONFLICT OF INTEREST / DISCLOSURE

None of the authors declared any conflict of interest.

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