# Caroli's Disease: Identification and Treatment Strategy

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Caroli's disease is a rare congenital disease of the liver characterized by cystic dilation of the intrahepatic bile duct. Classic Caroli's disease involves malformations of the biliary tract alone, whereas Caroli's syndrome refers to the presence of associated congenital hepatic fibrosis. Caroli's disease usually presents during childhood and early adulthood. The clinical features of Caroli's disease include jaundice, right upper abdominal pain, and fever due to the associated complications of hepatolithiasis or bacterial cholangitis. Endoscopic or percutaneous cholangiography is the traditional method of diagnosis, but magnetic resonance cholangiopancreatography is emerging as the diagnostic modality of choice. The treatment for Caroli's disease includes supportive care with antibiotics for cholangitis and ursodeoxycholic acid for hepatolithiasis. Surgical resection has been used successfully in patients with monolobar disease. For patients with diffuse involvement, the treatment of choice is orthotopic liver transplantation.

## Introduction

Caroli's disease, first reported in 1958 by Jacques Caroli [1], is a congenital cystic disorder of the liver characterized by dilation of the intrahepatic bile ducts. Classic Caroli's disease refers to involvement of the bile ducts alone. In the presence of associated periportal fibrosis (congenital hepatic fibrosis) and portal hypertension, it is often termed Caroli's syndrome [2,3]. Caroli's disease is also classified by Todani et al. [4] as type V choledochal cyst. The most common form of Caroli's disease is the diffuse form affecting both lobes of the liver [5]. Monolobar involvement is much more uncommon and when present involves the left lobe more often than the right [5,6] The condition often presents between the ages of 5 and 20 years, though manifestation in the neonatal period has also been described [7].

## Genetics and Pathogenesis

The embryonic basis for the development of Caroli's disease is the ductal plate malformation (DPM) leading to persistent embryonic bile ducts [8,9••]. In utero vascular accident has often been postulated to be the cause of the DPM. The level of involvement of the biliary tract by the DPM determines the anatomic manifestation of the cystic disease of the liver. DPM of the larger intrahepatic bile ducts leads to the development of Caroli's disease, whereas congenital hepatic fibrosis is a result of malformations at the level of the interlobular bile ducts [10]. Autosomal-recessive inheritance is most commonly proposed, but instances of the autosomal-dominant pattern have been reported in some families [11]. Parada et al. [12] identified an unbalanced translocation between chromosomes 3 and 8 (loss of 3p and gain of 8q) in the liver tissue of a patient with Caroli's disease and postulated that this could be involved in the pathogenesis of cholangiocarcinoma.

## Associated Syndromes

Caroli's disease has been associated with other inherited and acquired disorders, especially with cystic diseases of the kidney. Many cases of autosomal-dominant polycystic kidney disease have been reported in patients with Caroli's disease [10,13,14], with fewer reports of autosomal-recessive polycystic kidney disease [15] or medullary sponge kidney [10]. Caroli's disease has been reported in association with Lawrence-Moon-Biedl syndrome [16]. Systemic amyloidosis has also been reported in patients with Caroli's disease, possibly related to systemic inflammation from recurrent episodes of cholangitis [17].

## Diagnosis

### Cholangiography

The gold standard for diagnosis of Caroli's disease has traditionally been direct visualization of the biliary tract with endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). These studies allow ascertainment of a direct connection

between the cystic malformations of the liver and the biliary system, distinguishing this disease entity from isolated hepatic cysts. However, these procedures carry an associated risk of precipitating an episode of cholangitis and are increasingly replaced by noninvasive radiographic studies.

### Magnetic resonance imaging

Magnetic resonance cholangiopancreatography (MRCP) is emerging as the modality of choice for diagnosis of Caroli's disease [18–22]. The noninvasive nature of MRCP, along with its ability to diagnose parenchymal hepatic abnormalities and complications such as hepatolithiasis and malignancy, has solidified its use as the initial test for the diagnosis of Caroli's disease. Small case series have reported good accuracy with MRCP for the detection and classification of choledochal cysts [21]. The characteristic MRI appearance of Caroli's disease is the "string of beads" pattern of the ectatic intrahepatic bile ducts, or the "dot-sign," which refers to a cyst with a central or peripheral portal or hepatic artery branch within a pseudoseptum running through it [22]. By allowing for visualization of the entire biliary tract and the liver, MRCP also helps in identifying the extent and severity of the disease [20]. Park et al. [23] evaluated the accuracy of MRCP in diagnosing primary hepatolithiasis in 66 patients studied over a 2-year period. Compared with percutaneous cholangiography, MRCP had a sensitivity and specificity of 97% and 99%, respectively, in detecting intrahepatic stones. MRCP has also been found to be useful in the detection of cholangiocarcinoma in patients with choledochal cysts, with one study reporting a detection rate of 87% (13 of 15 patients) [21].

### Other imaging modalities

The central "dot-sign" appearance almost pathognomonic of Caroli's disease was first described on CT imaging [9••] and has also been described on ultrasonography [24]. Both remain good modalities for noninvasive imaging of suspected Caroli's disease; however, ultrasound may have limited ability to delineate abscesses, pancreatic fluid collections, or pseudocysts [25].

### Nuclear scintigraphy

A few case reports document hepatobiliary scintigraphy using $^{99}$mTc diethyl-iminodiacetic acid to diagnose Caroli's disease by revealing the characteristic beaded appearance of the intrahepatic bile ducts [26]. Scintigraphy might have a role in diagnosis of Caroli's disease, especially in patients who are not candidates to receive intravenous contrast agents, such as those with associated polycystic kidney disease.

## Complications

### Hepatolithiasis

Because of the relative rarity of Caroli's disease, data on the incidence of associated complications are limited. Hepatolithiasis is encountered in a third of the patients with Caroli's disease [27]. Although a majority of the stones are predominantly bilirubin stones [9••], analysis of the bile aspirates from the duodenum has also revealed supersaturation with cholesterol crystals [28]. Ursodeoxycholic acid (UDCA) has been used with the aim of treating and preventing future episodes of primary hepatolithiasis and cholangitis.

### Cholangitis

Bacterial cholangitis is the most common complication in Caroli's disease. It presents with fever, abdominal pain, and increased jaundice and in some cases can be severe, leading to liver abscess formation and sepsis. This complication can occur either spontaneously or in association with endoscopic or surgical intervention and may be recurrent [29]. In a series of 33 patients, Kassahun et al. [30•] reported that 20 (64.5%) had symptoms of right upper abdominal pain and fever, with 10 patients having jaundice. The presence of hepatolithiasis can predispose to biliary stasis, which increases the risk of cholangitis [31]. Intraductal stones should be extracted if possible, but cholangitis may persist in some cases [32]. Cholangitis should be treated with the standard antibiotics with adequate coverage for gram-negative organisms.

### Cancer

Generally, the risk of carcinoma in patients with Caroli's disease has been reported as 7% [33], but some authors have found higher rates in their series [32,34,35]. The bile stasis and associated chronic cholangitis predispose patients to the development of bile duct epithelium dysplasia and cholangiocarcinoma, the most common hepatobiliary malignancy in these patients, though cases of hepatocellular carcinoma and gallbladder cancer have also been reported [32]. Although some authors have postulated that resection for monolobar involvement decreases the risk of cancer [36], cholangiocarcinoma has been reported even after surgical treatment for monolobar disease with resection [2,30•,32]. Three patients in the series by Kassahun et al. [30•] had progression of cholangiocarcinoma or recurrence of their disease after resection, and one patient in the series by Ammori et al. [2] developed cholangiocarcinoma after surgical treatment and eventually required orthotopic liver transplantation (OLT).

### Portal hypertension

Caroli's syndrome (associated congenital hepatic fibrosis) is often complicated by portal hypertension that presents with splenomegaly, ascites, and variceal bleeding in early childhood. Variceal bleeding in these patients should be managed in a similar manner as for other causes of variceal enlargement, with endoscopic band ligation or sclerotherapy. Beta-blockers are recommended for prophylaxis of bleeding [9••]. Transjugular intrahepatic portosystemic shunt placement and liver transplantation

are also options for patients with significant disease or refractory bleeding.

## Treatment

### UDCA

UDCA is used to treat and prevent future episodes of primary hepatolithiasis and cholangitis in patients with Caroli's disease. Ros et al. [28] reported on 17 patients with Caroli's syndrome with primary intrahepatic stones who were treated with UDCA. A majority of the stones were cholesterol rich in composition. All patients achieved sustained remission within 2 months of therapy. Follow-up ultrasound showed complete ($n$=3) or partial ($n$=9) clearance of the stones with normalization of the liver function tests. All but the two patients who were noncompliant with UDCA treatment remained free of biliary pain or cholangitis. UDCA is also used in conjunction with other modes of therapy, such as extracorporeal shock-wave lithotripsy (ESWL) [37].

### Therapeutic endoscopy

Although the risk of cholangitis theoretically increases with ERCP, cases in which Caroli's disease has been managed successfully with endoscopic intervention have been reported [5,6,37–39]. Ciambotti et al. [5] described a patient with unilobar Caroli's disease who underwent ERCP, endoscopic sphincterotomy, and stent placement for hepatolithiasis in conjunction with UDCA therapy. Caroli-Bosc et al. [37] described six patients with hepatolithiasis with or without cholangitis who underwent therapeutic ERCP; four also underwent endoscopic sphincterotomy, one had surgical sphincteroplasty, and four had ESWL or intraductal electrohydraulic lithotripsy (IEL). These authors did not see an increase in cholangitis in this group of patients. They also suggest that patients with frequent cholangitis should undergo endoscopic surveillance every 6 to 12 months on the assumption that cholangitis is intimately related to hepatolithiasis, which causes biliary dilation [37]. However, in patients with infrequent episodes of cholangitis, endoscopic surveillance might not be indicated or may be needed at less frequent intervals. In such patients the risk of procedure-related cholangitis must be balanced against the risk of complications arising from the natural history of the disease. In another case series, Naga and Suleiman [38] described three patients with bilobar Caroli's disease who underwent endoscopic sphincterotomy and stone extraction or stenting. One patient was lost to follow-up; another did well at 4 years, and the third patient, who had associated cholangiocarcinoma, died after 5 months. Although endoscopic drainage may decrease the frequency of cholangitis, its role in reducing the risk of subsequent development of cholangiocarcinoma is still doubtful [40]. Hepatolithiasis and recurrent cholangitis remain the most frequent indications for therapeutic endoscopy. Chalasani et al. [6] reported a patient with Crohn's disease who had a spontaneous rupture of the biliary duct that was managed with endoscopic stent placement.

### Surgery

Surgical resection (partial hepatectomy; lobectomy) remains a good option for segmental or unilobar involvement in Caroli's disease without the risk of immunosuppression associated with liver transplantation [30•,41,42]. Case series from several institutions have described successful treatment of unilobar disease with resection [2,30•,39,41,43–46]. Ammori et al. [2] described four patients with Caroli's disease (3 segmental, 1 multilobar) who received surgical treatment. The three patients with segmental disease underwent resection; however, the disease recurred in the remaining liver in two of the patients. One patient with bilobar disease underwent hepatic trisectomy but subsequently died from portal hypertensive variceal bleeding. Orozco et al. [43] described two patients who underwent partial hepatectomy with no recurrent disease 3 and 5 years postoperatively. One of the largest series involving resection for the treatment of Caroli's disease was by Kassahun et al. [30•] from Leipzig, Germany. They described 27 patients who underwent liver resection with or without biliodigestive anastomosis for localized Caroli's disease. They determined the need for hepaticojejunostomy by the extent of disease with or without hilar involvement. Nearly 75% of the patients had received previous nonsurgical treatment with antibiotics (71%) or UDCA (74%). The majority of the patients (87.2%) did not have significant postoperative complications. Eighty-four percent (including two who received OLT) remained free of biliary symptoms over a median follow-up period of 3.7 years.

### Liver transplantation

Liver transplantation is the only modality of treatment available for patients with Caroli's disease that is not confined to one segment or lobe of the liver. One of the earliest reports of OLT for Caroli's disease was by Sans et al. [29] in 1997, who described two patients with Caroli's disease with recurrent cholangitis who successfully underwent OLT. Since that time, other case reports have documented successful treatment of multilobar Caroli's disease with OLT [2,29,45,47,48•,49,50]. Habib et al. [48•] studied 30 patients with Caroli's disease who underwent OLT. Nine of the patients had associated congenital hepatic fibrosis. They reported approximately 50% graft survival 4000 days after transplant and higher overall patient survival over the same follow-up period. However, patients with associated congenital hepatic fibrosis had worse survival. Just prior to the publication of the previously described series, De Kerckhove et al. [47] reviewed 22 previously reported cases of OLT performed for Caroli's disease and analyzed the European transplant registry for the 110 patients who received OLT for Caroli's disease. Five-year

graft survival was established in 68%, and 76% of the patients survived at 5 years.

No consensus has been reached on the indication or timing of OLT for patients with Caroli's disease. The majority of the patients in the series by Habib et al. [48•] had signs of hepatic decompensation, defined as ascites, encephalopathy, coagulopathy, portal hypertension, jaundice, prolonged prothrombin time, or decreased albumin. However, other series have reported recurrent cholangitis as the primary indication for OLT [29,47].

## Conclusions

Caroli's disease is a congenital hepatic cystic disease that may be associated with congenital hepatic fibrosis. It presents in early childhood with symptoms of hepatolithiasis or recurrent cholangitis. Recent literature supports the use of MRCP as an initial diagnostic tool for Caroli's disease. MRCP is supplanting endoscopic or percutaneous cholangiography because it is noninvasive and helpful in the identification of associated liver pathology and complications of Caroli's disease. Although ERCP for biliary decompression in cases of cholangitis is clearly warranted, its role in surveillance for cholangiocarcinoma and prophylactic treatment of hepatolithiasis remains to be defined. Successful segmental hepatic resection has been reported from multiple centers in monolobar Caroli's disease. For patients with diffuse disease, OLT remains the only treatment option.

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