Caroli disease

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INTRODUCTION

Caroli disease is a congenital disorder characterized by multifocal, segmental dilatation of large intrahepatic bile ducts [1,2]. The condition is usually associated with renal cystic disease of varying severity. This topic will review the clinical manifestations, diagnosis, and management of Caroli disease.

TERMINOLOGY

Caroli initially described two distinct disease entities characterized by segmental, saccular dilatations of the **large intrahepatic** bile ducts [3,4].

- Caroli disease – This is characterized by bile ductular ectasia without other apparent hepatic abnormalities.
- Caroli syndrome – Intrahepatic bile duct dilatation is associated with congenital hepatic fibrosis [5].

EPIDEMIOLOGY AND PATHOGENESIS

Prevalence — Caroli disease is rare and is estimated to affect 1 in 1,000,000 individuals. Caroli syndrome is a more common variant than Caroli disease and has an estimated prevalence of 1

in 100,000 individuals [6].

Genetics — Caroli syndrome is associated with autosomal recessive polycystic kidney disease (ARPKD) caused by pathogenic variants in the *PKHD1* gene. The polycystic kidney and hepatic disease 1 (*PKHD1*) gene, mapped to chromosome 6 (6p21-p12), encodes for fibrocystin, a large integral membrane protein [7]. This protein shares structural features with the hepatocyte growth factor receptor, localizes to cilia, and appears to belong to a superfamily of proteins that involve numerous cellular functions including regulation of cell proliferation, differentiation, cell adhesion and repulsion, tubulogenesis, cell polarity, and cell matrix interactions [8-10]. *PKHD1* is expressed primarily in the kidneys with lower levels in the liver, pancreas, and lungs, a pattern consistent with the phenotype of the disease, which primarily affects the liver and kidneys.

Disease variants in either of two different genes (*PKD1* or *PKD2*), which are associated with autosomal dominant polycystic kidney disease (ADPKD), have also been associated with Caroli disease in rare instances [11]. The protein products of the *PKD* genes (polycystin-1 and polycystin-2) are thought to interact as part of a multiprotein membrane-spanning complex involved in cell-cell or cell-matrix interactions [12,13]. Polycystin-1 is expressed in the fetal kidney and liver, including the biliary system, and is likely involved in the embryogenesis of these organs.

Pathogenic variants in the *WDR19* gene have been associated with nephronophthisis (NPHP), an autosomal recessive cystic kidney disorder that typically progresses to end-stage kidney disease (ESKD) and Caroli syndrome or disease. The *WDR19* gene encodes for a protein required for retrograde ciliary transport [14].

In addition, Caroli disease and syndrome have also been associated with other hepatorenal fibrocystic diseases including Meckel-Gruber syndrome, COACH (cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis) syndrome, Joubert syndrome and related disorders, Bardet–Biedl syndrome, and oral-facial-digital syndrome.

Pathophysiology — The molecular pathogenesis of Caroli disease and syndrome is incompletely understood. The proteins that are defective in most of the fibrocystic diseases of the liver and kidney are expressed on the primary cilia and centrosome complex of renal tubule cells and cholangiocytes [15]. Primary cilia are non-motile, microtubule-based organelles that are found on the luminal surface of many differentiated epithelial cells. They sense mechanical, chemical, and osmotic stimuli associated with luminal fluid flow and transmit these signals to a variety of intracellular signal transduction pathways, involving mediators such as intracellular calcium and cyclic adenosine monophosphate. Urine and bile composition is thought to be modified as a result of cilia-based signaling. Ciliary function is also essential for normal

development of the liver and biliary system through effects on cell proliferation and maintenance of planar cell polarity.

The pathogenesis of the intrahepatic ductal dilatation and hepatic fibrosis appears to be related to an arrest or derangement in remodeling of the ductal plate of the larger intrahepatic bile ducts during development [16]. In congenital hepatic fibrosis, a genetically determined dysfunction of cholangiocyte homeostasis promotes the secretion of chemokines able to recruit macrophages that orchestrate a pro-fibrotic tissue response [17]. It is also hypothesized that if the specific genetic abnormality leading to abnormal remodeling of the ductal plate exerts its influence during an early period of bile duct embryogenesis, Caroli disease results [3]. However, if abnormal remodeling occurs later in embryogenesis, it results in abnormalities in the peripheral biliary ramifications (the intralobular bile ducts) leading to Caroli syndrome.

CLINICAL MANIFESTATIONS

Signs and symptoms — Symptoms of Caroli disease usually occur in early adulthood, with greater than 80 percent of patients presenting before the age of 30 years. Patients present with fever, jaundice, and abdominal pain due to cholangitis. Patients with acute cholangitis can also present with complications including hepatic abscess, sepsis, multiple organ system dysfunction, and shock. Other patients may present with only intermittent abdominal pain or pruritus due to cholestasis. (See "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'Clinical manifestations'.)

Patients with Caroli syndrome may present with acute cholangitis or symptoms of non-cirrhotic portal hypertension and its sequelae, such as acute upper gastrointestinal bleeding due to esophageal variceal hemorrhage [4]. In the late stages of the disease, or following an episode of gastrointestinal bleeding, patients will occasionally develop jaundice, ascites, or hepatic encephalopathy. Children with Caroli syndrome usually have an earlier onset of symptoms and a more rapidly progressive disease. Infants may present with cholestasis. On physical examination, the liver is frequently enlarged and the spleen becomes palpable as portal hypertension develops. (See "Noncirrhotic portal hypertension", section on 'Clinical manifestations'.)

Juvenile nephronophthisis and medullary cystic disease have been observed, although they are probably rare [18]. (See "Autosomal recessive polycystic kidney disease in children" and "Approach to evaluation of cholestasis in neonates and young infants".)

Laboratory studies — Patients with Caroli disease and Caroli syndrome may have a cholestatic pattern of liver injury with a predominant elevation of serum alkaline phosphatase, gamma-glutamyl transpeptidase, and bilirubin (predominantly conjugated) concentration. In addition to a cholestatic pattern of liver test abnormalities, patients with acute cholangitis have an elevated white blood cell count with neutrophil predominance. However, a pattern of acute hepatocyte necrosis can be seen in which the aminotransferases may be as high as 2000 IU/L. (See "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'Laboratory tests'.)

Coagulopathy from vitamin K malabsorption may occur in patients with chronic cholestasis. Hepatic synthetic function, as measured by serum albumin and international normalized ratio, is well preserved initially, but may be affected by progressive liver damage due to recurrent cholangitis and biliary obstruction. (See "Tests of the liver's biosynthetic capacity (eg, albumin, coagulation factors, prothrombin time)".)

Complications — Approximately 30 percent of patients with Caroli disease have intrahepatic stones that predispose to recurrent episodes of cholangitis. Repeated episodes of acute cholangitis can result in secondary biliary cirrhosis. (See "Recurrent pyogenic cholangitis", section on 'Acute complications'.)

The risk of cholangiocarcinoma is increased in patients with Caroli disease and Caroli syndrome, with an incidence of up to 7 percent in case series [19]. The increase in risk may be secondary to bile stasis and the presence of high concentrations of unconjugated secondary bile salts. Cholangiocarcinoma is rare in childhood, with an increase in incidence with age. Unexplained rapid clinical deterioration with jaundice, weight loss, and abdominal pain, or the appearance of a new biliary stricture, should prompt evaluation for cholangiocarcinoma [19]. Evaluation of patients with suspected cholangiocarcinoma is discussed in detail separately. (See "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'Suspected intrahepatic cholangiocarcinoma'.)

Amyloidosis has also been described due to the inflammation from chronic or recurrent cholangitis [20]. (See "Overview of amyloidosis" and "Overview of amyloidosis", section on 'Clinical manifestations'.)

DIAGNOSIS

The diagnosis of Caroli disease is made incidentally by ultrasound or magnetic resonance cholangiopancreatography (MRCP) that demonstrates cystic dilation of the large proximal intrahepatic bile ducts with a normal common bile duct in a patient with acute cholangitis or

elevated liver tests. The presence of Caroli syndrome is based on the additional presence of portal hypertension (manifested by esophageal and/or gastric varices, portal hypertensive bleeding and/or portosystemic shunting on imaging).

Diagnostic imaging — In patients with Caroli disease/Caroli syndrome, abdominal imaging (ultrasonography, computed tomography [CT] scan, magnetic resonance cholangiography) findings include bile duct ectasia and irregular, cystic dilation of the large proximal intrahepatic bile ducts with a normal common bile duct (picture 1) [21-23]. In addition, a "central dot sign," defined as a small foci of strong contrast enhancement within dilated intrahepatic ducts, may be seen on CT or magnetic resonance imaging [24]. While the segmental bile ducts are predominantly involved, the dilated portions are in continuity with the rest of the biliary tract. The disease may be limited to one lobe of the liver, most commonly the left lobe. Imaging studies can also demonstrate the renal features of polycystic kidney disease [25].

Liver biopsy in selected patients — A liver biopsy is not required to establish a diagnosis of Caroli syndrome and carries increased risk in the setting of cystic dilatation of the biliary system. However, in patients with Caroli syndrome presenting with an enlarged, hard liver with features of portal hypertension and without findings of biliary dilatation or kidney disease, histologic findings on liver biopsy can support the diagnosis. In Caroli syndrome, histologic features include broad bands of mature fibrosis, distorted bile duct structures, and enlargement of portal tracts. There may also be hypoplasia of the portal vein branches. In patients with concurrent cholangitis, an acute and chronic inflammatory cell infiltrate may be present around the dilated bile ducts. (See "Noncirrhotic portal hypertension", section on 'Diagnosis'.)

Differential diagnosis

- **Liver abscess** – Patients with a liver abscess can present with right upper quadrant pain, elevated liver transaminases, or hyperbilirubinemia. Ultrasound and CT can differentiate between a liver abscess and acute cholangitis due to Caroli disease. (See "Pyogenic liver abscess", section on 'Imaging'.)

- **Polycystic liver disease** – Demonstration of communication between sacculi and bile ducts on abdominal imaging is important in distinguishing Caroli disease from polycystic liver disease. (See "Autosomal dominant polycystic kidney disease (ADPKD): Extrarenal manifestations", section on 'Hepatic cysts'.)

MANAGEMENT

Treatment is largely supportive and is based on the clinical presentation.

General measures in all patients

- Patients should be monitored for deficiency in fat-soluble vitamins due to chronic cholestasis [26,27]. We obtain laboratory tests for vitamins A, D and E, and prothrombin time, annually. (See 'Laboratory studies' above.)

- Low bone mass (osteopenia) may be a cause of morbidity in adults and children with cholestatic liver disease. In the absence of symptomatic fractures, decreased bone mineral density may not be clinically evident. We perform bone mineral density testing by dual-energy X-ray absorptiometry (DXA) analysis in patients with chronic cholestasis and at least one additional risk factor for osteoporosis (table 1).

Patients with choledocholithiasis and cholangitis — The management of patients with acute cholangitis is with supportive care, antibiotics, and biliary drainage. Because of bile stasis and the presence of intrahepatic lithiasis, infection may be particularly difficult to eradicate and can be associated with progressive deterioration of liver function. Patients may require prolonged courses of antibiotics. (See "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'Management'.)

Endoscopic, percutaneous, and combined techniques have been used to clear intrahepatic stones and provide biliary drainage. The choice among these should be guided by specific anatomic considerations in individual patients and the availability of expertise. Endoscopic sphincterotomy and stone extraction can be used to remove common bile duct stones but the extraction of intrahepatic stones is far more difficult [28]. In one study, endoscopic sphincterotomy followed by either extracorporeal shock-wave lithotripsy or intraductal electrohydraulic lithotripsy was successful in clearing intrahepatic stones in four of six adults and partially in another two [29]. Per oral cholangioscopy using a mother-daughter endoscope system was successful in 23 of 36 patients (60 percent) in another report of patients with hepatolithiasis [30]. Long-term follow-up of these patients suggested that stone clearance can be durable. (See "Recurrent pyogenic cholangitis", section on 'Clearance of stones'.)

Laser lithotripsy permits precise targeting of intrahepatic stones, thereby reducing the risk of bile duct injury, but is not widely available. (See "Cholangioscopy and pancreatoscopy" and "Laser lithotripsy for the treatment of bile duct stones".)

Dissolution therapy using synthetic bile salts has also been described. In one of the largest series, for example, ursodeoxycholic acid (10 to 20 mg/kg per day for a mean of 48 months) was associated with complete dissolution of intrahepatic stones in three patients and partial

dissolution in another nine [31]. Ursodeoxycholic acid works probably by increasing bile flow and decreasing bile stasis rather than by dissolving the stones, since most stones are pigmented. (See "Recurrent pyogenic cholangitis", section on 'Clearance of stones'.)

Surgery in selected patients

Partial hepatectomy — Partial hepatectomy may be curative in selected patients in whom the disease is confined to a single lobe of the liver [32-35]. In a retrospective study of 111 patients who underwent liver resection for Caroli disease or Caroli syndrome (approximately 90 percent involved the left lobe of the liver), the 5- and 10-year survival rates were 89 and 82 percent, respectively [36].

Liver transplant — Patients who have recurrent bouts of biliary infection, particularly those who also have complications related to portal hypertension, may require liver transplantation [33,37-39]. In a retrospective study in which transplant outcomes were compared in 140 patients with Caroli disease or syndrome to 4797 patients with primary biliary cholangitis, 489 patients with secondary biliary cirrhosis, 6033 patients with primary sclerosing cholangitis, and 92,210 patients post-orthotopic liver transplantation, patient and graft survival in patients with Caroli disease or syndrome was comparable to or better than that of patients transplanted for other diseases [39].

Screening for complications in patients with Caroli syndrome — In patients with Caroli syndrome, management should also include the prevention and treatment of the consequences of portal hypertension (predominantly variceal bleeding).

Esophageal varices — Patients should be screened for esophageal varices with upper endoscopy. While data are limited in this population regarding the best approach to management, patients are typically managed in the same manner as those with portal hypertension due to cirrhosis, and screening is repeated based on the presence and size of varices. Primary and secondary prevention of variceal bleeding include the use of nonselective beta blockers and endoscopic variceal ligation. A selective shunting procedure can provide relief from portal hypertension since liver function may be well preserved. However, a transjugular intrahepatic portosystemic shunt may be hazardous because of cystic dilatations of the biliary tree. (See "Primary prevention of bleeding from esophageal varices in patients with cirrhosis".)

Portal vein thrombosis — Patients with portal hypertension should also undergo screening for portal vein thrombosis with Doppler ultrasonography every six months.

PROGNOSIS

The prognosis is variable depending upon the severity of disease and the presence of coexisting renal dysfunction. Recurrent infections and other complications related to intrahepatic stones is associated with significant morbidity.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatic and biliary cysts".)

SUMMARY AND RECOMMENDATIONS

- **Terminology**
  - Caroli disease is characterized by bile ductular ectasia without other apparent hepatic abnormalities.
  - Caroli syndrome is characterized by bile duct dilatation associated with congenital hepatic fibrosis. (See 'Terminology' above.)
- **Epidemiology and pathogenesis** – Caroli disease is rare and is estimated to affect 1 in 1,000,000 individuals. Caroli syndrome is a more common variant than Caroli disease and has an estimated prevalence of 1 in 100,000 individuals. The molecular pathogenesis of Caroli disease and syndrome is incompletely understood. Most cases are transmitted in an autosomal recessive fashion and are associated with autosomal recessive polycystic kidney disease (ARPKD). (See 'Epidemiology and Pathogenesis' above.)
- **Clinical manifestations** – Symptoms of Caroli disease usually occur in early adulthood, with greater than 80 percent of patients presenting before the age of 30 years. Patients present with fever, jaundice, and abdominal pain due to cholangitis. The clinical manifestations of Caroli syndrome are related both to the biliary abnormalities and portal hypertension from congenital hepatic fibrosis. There are several modes of presentation depending on the age of onset and the predominance of hepatic or renal involvement. Patients with Caroli syndrome may present with acute cholangitis or symptoms of non-cirrhotic portal hypertension and its sequelae, such as acute upper gastrointestinal bleeding due to esophageal variceal hemorrhage. (See 'Clinical manifestations' above.)

- **Diagnosis** – The diagnosis of Caroli disease is made incidentally by ultrasound or magnetic resonance cholangiopancreatography that demonstrates cystic dilation of the large proximal intrahepatic bile ducts with a normal common bile duct in a patient with acute cholangitis or elevated liver tests (picture 1). The presence of Caroli syndrome is based on the additional presence of portal hypertension (manifested by esophageal and/or gastric varices, portal hypertensive bleeding and/or portosystemic shunting on imaging). (See 'Diagnosis' above.)

- **Management** – Management is based on the clinical presentation. (See 'Management' above.)

  - **Monitoring for complications of cholestasis** – Patients should be monitored for deficiency in fat-soluble vitamins and osteopenia due to chronic cholestasis. We obtain laboratory tests for vitamins A, D and E, and prothrombin time, annually. We also perform bone mineral density testing by dual-energy X-ray absorptiometry (DXA) analysis in patients with chronic cholestasis and at least one additional risk factor for osteoporosis. (See 'General measures in all patients' above.)

  - **Patients with acute cholangitis** – Similar to patients with acute cholangitis due to other causes, treatment of acute cholangitis in patients with Caroli disease includes supportive care, antibiotics, and biliary drainage. Endoscopic, percutaneous, and combined techniques have been used to clear intrahepatic stones and provide biliary drainage. The choice among these should be guided by specific anatomic considerations in individual patients and the availability of expertise. Liver transplantation is reserved for patients who have recurrent bouts of biliary infection, particularly those who also have complications related to portal hypertension. (See "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'General measures' and "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'Biliary drainage' and 'Patients with choledocholithiasis and cholangitis' above.)

  - **Screening for portal hypertension** – In patients with Caroli syndrome we perform periodic upper endoscopy to screen for esophageal varices and Doppler ultrasonography every six months to screen for portal vein thrombosis. (See 'Screening for complications in patients with Caroli syndrome' above.)

- **Prognosis** – The prognosis is variable depending upon the severity of disease and the presence of coexisting renal dysfunction. (See 'Prognosis' above.)

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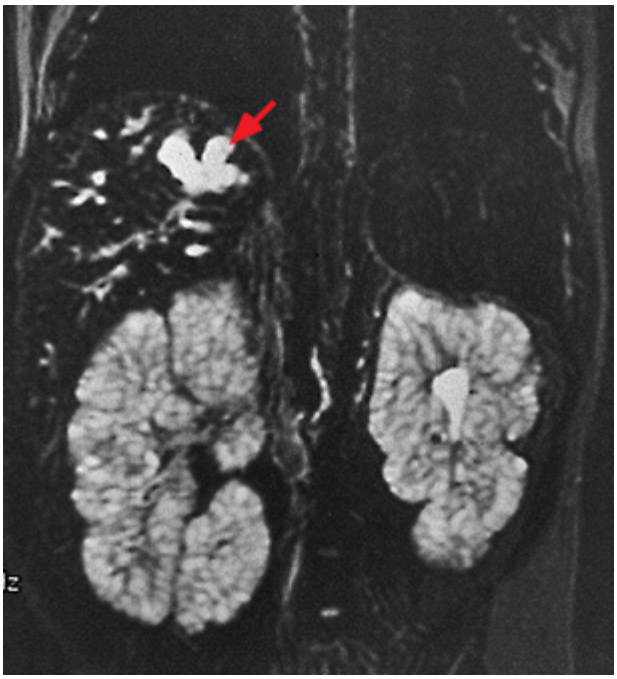
GRAPHICS

Caroli's disease



Magnetic resonance cholangiography in an infant with Caroli's disease. There is biliary ectasia throughout the liver and saccular dilatation of bile ducts in the left lobe (arrow). The kidneys show typical changes of autosomal recessive polycystic kidney disease with massive enlargement due to fusiform dilatation of the collecting ducts.

Courtesy of Frederick J Suchy, MD.

Graphic 71092 Version 1.0

Clinical risk factors for fracture independent of bone mineral density

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption

Rheumatoid arthritis
Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Data from: Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005; 16:581.

Graphic 76445 Version 4.0

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