

Caroli's Disease: A Mini-Review

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1. Abstract

Caroli's disease is a rare congenital condition that is characterised by intrahepatic biliary duct dilatation without fibrosis. It is associated with an increased risk of cholelithiasis, cholangitis and cholangiocarcinoma. As such, it is an important clinical entity to be aware of. Most of the literature surrounding Caroli's disease is limited to case reports and case series. This review will explore the clinical characteristics, imaging modalities and management of Caroli's disease.

2. Introduction

Caroli's Disease (CD) is a rare congenital condition involving dilatations of the large intra-hepatic bile ducts. It is classified as a type V congenital bile duct cyst as per the Todani classification [1]. CD is distinct from Caroli's Syndrome (CS). When intra-hepatic biliary dilatation is seen in the presence of congenital hepatic fibrosis, the condition is termed Caroli's syndrome; intra-hepatic biliary dilatation without hepatic fibrosis is Caroli's disease. The intra-hepatic dilatation can be unilobar or bilobar. A systematic review demonstrated 56.5% of described cases having bilobar distribution [2]. A recently published multicentre radiological study also demonstrated a preponderance for bilobar CD, with 68.2% of cases diagnosed by magnetic resonance cholangiopancreatography (MRCP) being bilobar [3]. When biliary dilatation is unilobar, it more commonly occurs in the left lobe of the liver [4].

CD is an extremely rare clinical entity, with an estimated incidence of 1:1,000,000 in the population. There is a similar incidence of CD between sexes [2]. Patients can present in the neonatal period through to adulthood, but the average age of diagnosis for CD is between the second and third decades of life, with more than 80% of patients presenting before turning 30 years of age [5, 6].

3. Genetics and Pathophysiology

CD and Caroli's syndrome typically have an autosomal recessive inheritance [7]. The pathophysiology of CD is not completely understood, but is thought to be secondary to a loss of function mutation in the polycystic kidney and hepatic disease 1 (PKHD1) gene [8]. The PKHD1 gene encodes fibrocystin. Deficiency of fibrocystin results in abnormal embryogenesis of the biliary ductal system causing the cystic dilatations seen in CD [8].

4. Clinical Presentation

The presentation of CD is variable and, given its low prevalence in the population, a range of presentations have been reported in the literature. It is typically characterised by recurrent episodes of cholangitis, with patients presenting with jaundice, right upper quadrant pain and fevers [6]. The intra-hepatic dilatation in CD predisposes to biliary stasis and sludge formation. This results in hepatolithiasis and obstruction leading to cholangitis. Another consequence of intrahepatic cholestasis is hyperbilirubinaemia, which may present as pruritus and jaundice [6]. In a retrospective study of 17 patients, the presenting complaint was right upper quadrant pain in 6 patients, right upper quadrant pain and fever in 4 patients, clinical signs of liver failure in 3 patients, fever in 2 patients and jaundice in 2 patients [9]. Correia and Morgado reported two cases with atypical presentations of chronic epigastric pain [10].

5. Diagnosis/Work-up

Examination findings in CD are non-specific [6]. Right upper quadrant tenderness with a negative Murphy's sign is typically present and may be associated with hepatomegaly. Scleral icterus may be seen due to the presence of hyperbilirubinemia. If cirrhosis is present, clinical findings such as spider naevi, hepatosplenomegaly and ascites can be found.

Blood tests can demonstrate leukocytosis if the patient presents with cholangitis. The most commonly deranged liver function tests are an elevated alkaline phosphatase and gamma glutamyl transferase, depicting an obstructive pattern [6]. Hepatic synthetic function is usually preserved, with normal albumin and coagulation tests. α -fetoprotein and CA19-9 levels should be assessed, as they may be elevated in the presence of cholangiocarcinoma.

Multiple imaging modalities can be useful in diagnosing CD, including ultrasound, Computed-Tomography (CT), MRI and cholangiography. Ultrasound is a low-risk and accessible modality that may demonstrate dilated intrahepatic bile ducts, any intraductal calculi, as well as assess for liver cirrhosis. The characteristic appearance of CD on ultrasound is of intrahepatic cysts with intraductal septa or fibrovascular bundles. Doppler ultrasonography would reveal that these fibrovascular bundles consist of portal veins and hepatic arteries [7].

CT scans can be diagnostic for CD and are typically characterised by multiple hypodense round lesions in continuity with the dilated intrahepatic bile ducts. The “central dot” sign is pathognomonic for CD, involving contrast-enhancing dots within the dilated intrahepatic bile ducts that represent fibrovascular bundles [7].

The gold standard for diagnosis of CD has been cholangiography, allowing direct visualisation of the biliary tract by Percutaneous Transhepatic Cholangiogram (PTC) or Endoscopic Retrograde Cholangiography (ERCP). Cholangiography demonstrates alternating areas of focal stenosis and saccular dilatation of intrahepatic bile ducts that can be localised or diffuse throughout the liver [9]. In a retrospective study by Levy et al., 82% of patients had segmental rather than diffuse dilatation [9]. Cholangiography can also identify intraductal stones, seen as filling defects. However, invasive cholangiography is associated with an increased infection risk, which is a significant concern considering CD patients are already predisposed to cholangitis. As such, it is reserved for confirming doubtful cases.

MRCP has mostly replaced PTC and ERCP due to its non-invasive nature, avoiding the increased risk of cholangitis. A systematic review by Vacca-Carvajal et al. demonstrated that MRI was the most commonly used diagnostic tool for CD, utilised in 73.8% of cases [2]. MRCP is also able to diagnose complications such as lithiasis and cholangiocarcinoma, making it the preferred imaging modality for diagnosis of CD [7]. The characteristic MRI findings in CD is the “string of beads” pattern of the intrahepatic bile ducts, or the “dot sign” which corresponds to a fibrovascular bundle within the cystic biliary dilatation [9, 11]. The “dot sign” is best visualised on a T1 MRI with contrast enhancement. Lewin et al. demonstrated the “dot sign” in 22.7% of patients with CD all of whom had diffuse disease [3]. MRCP has a 97% sensitivity and 99% specificity for detecting intrahepatic stones [11]. Interestingly, intrahepatic biliary calculi have been demonstrated to occur more frequently in unilobar CD [3].

MRCP is also useful in detecting cholangiocarcinoma, with one study demonstrating a detection rate of 87% of cholangiocarcinoma in patients with choledochal cysts [11].

In patients who are not able to receive intravenous contrast due to renal impairment or allergy, a nuclear medicine scan can be performed. This may demonstrate a beaded appearance of intrahepatic bile ducts [11].

6. Management of Caroli's Disease

Management of CD ranges from medical management to liver transplantation. Medical therapy involves ursodeoxycholic acid with the aim of reducing cholestasis. It acts to decrease hepatic synthesis, secretion and intestinal absorption of cholesterol, resulting in reduced bile viscosity [11]. Appropriate broad-spectrum antibiotics should be used in episodes of cholangitis.

Endoscopic management has been reported to be successful in CD. ERCP can be used to clear ductal stones and for stent placement. In a case series by Caroli-Bosc et al., 6 patients underwent therapeutic ERCP with endoscopic sphincterotomy, resulting in successful clearance of intrahepatic stones, and only 2 patients had further episodes of cholangitis in the follow-up period (mean 6.2 years) [12].

Surgical resection, either partial hepatectomy or lobectomy, is the main treatment option for localised CD. In a large case series by Kassahun et al. of 27 patients who underwent liver resection for localised CD, 84% of patients remained free of biliary symptoms for a median follow-up period of 3.7 years [13]. A multicentre study from Argentina demonstrated no mortality and complete symptom resolution in 24 patients following surgical resection after a median follow-up of 166 months [14]. Minimally invasive surgery is a recent advance in CD management. A recent case series of 7 patients with unilobular CD demonstrated that laparoscopic liver resection is a feasible option for these patients [15].

Liver transplantation is the only curative modality for CD that is not localised to one segment or lobe of the liver. The indications for transplantation in patients with CD are not well-defined, with some patients undergoing transplantation for recurrent cholangitis whereas other cases are following liver failure [11]. Lai and Lerut proposed that liver transplantation should be utilised in patients with bilobar disease or unilobar disease with portal hypertension, and that it may also have a role in patients with small concurrent cholangiocarcinoma [16]. In patients undergoing liver transplantation for CD, the 1-year, 3-year, and 5-year graft (79.9, 72.4 and 72.4 %) and patient survival rates (86.3, 78.4, and 77 %) are high in patients undergoing liver transplantation for CD, supporting the use of this therapy [17]. Additionally, liver transplantation eliminates the risk of cholangiocarcinoma transformation.

7. Follow-Up

CD is associated with an increased risk of cholangiocarcinoma. The risk of cholangiocarcinoma in patients with CD is reported to be

100 times higher than the general population [18]. In a systematic review, Fahrner et al. demonstrated the quoted incidence of cholangiocarcinoma ranged from 2.7% to 37.5% with an overall incidence of 6.6% (19). Furthermore, they demonstrated a high recurrence rate of cholangiocarcinoma of up to 75% and an overall 1-year survival rate of 36% in patients with cholangiocarcinoma [19]. A recent multicenter German study reported a similar incidence of cholangiocarcinoma, with 6.3% of patients demonstrating malignancy following surgical resection for CD [20]. The difficulty with surveillance for cholangiocarcinoma in patients with CD is that CA 19-9 is also elevated with biliary obstruction and cholangitis. However, in the absence of other markers, it is reasonable to perform regular surveillance with tumour markers (AFP and CA 19-9) and imaging modalities (ultrasound and MRI), although no guidelines exist regarding the timeframe.

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