Caroli's Disease

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5.1 Introduction

Caroli's disease was described for the first time in 1958 by a French gastroenterologist, Jacques Caroli. It is an autosomal recessive congenital disease, with an estimated incidence of 1:1,000,000 and higher prevalence in females.

Among biliary system non-neoplastic pathology, cystic disease represents a rare congenital condition. Todani's classification of bile duct cysts describes five main groups of cysts depending on intra- and/or extrahepatic bile ducts involvement. Caroli's disease is also referred to as type V bile duct cysts according to this classification.

The five main groups of Todani's classification are:

- **Type I**, choledochal cyst. It is the most frequent form (80–90%) and is thought to be due to an anomalous pancreatic-biliary junction, which results in a reflux of pancreatic secretion into the bile duct. The dilatation may extend to the entire extrahepatic duct (Ia) or be segmental (Ib) or fusiform (Ic).
- **Type II**, supraduodenal extrahepatic bile duct diverticulum. It accounts for 3% of all bile duct cysts.
- **Type III**, choledochocele, intramural segment dilatation, observed in 5% of cases and responsible of recurrent biliary colic or pancreatitis.

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- **Type IV**, consists of intra- and extrahepatic (IVa) or extrahepatic only (IVb) bile ducts multiple dilatations, present in 10% of cases.
- **Type V**, known as Caroli Disease (CD) and characterized by multiple intrahepatic cystic dilatation.

5.2 Pathogenesis

CD is the result of an abnormal development of the ductal plate, a transient structure that appears at the sixth week of fetal life. From the 12th week to the end of the gestation or the very first postnatal period, the remodeling and partial involution of the ductal plate forms the biliary tree. The remodeling of the ductal plate starts from the hepatic hilum and progresses toward the periphery: the partial or complete interruption of this process may cause congenital cystic lesion formation, with different phenotypes depending on the stage in which the defect occurs (Fig. 5.1). The so-called *fibro-polycystic liver diseases* include:

1. Large bile ducts involvement: *Caroli's disease* (intrahepatic bile ducts involvement) or *choledochal cyst* (extrahepatic bile ducts involvement)
2. Medium bile ducts involvement: *autosomal dominant polycystic liver disease* (ARPKD)
3. Small bile ducts involvement: *biliary hamartomas* or *congenital hepatic fibrosis*

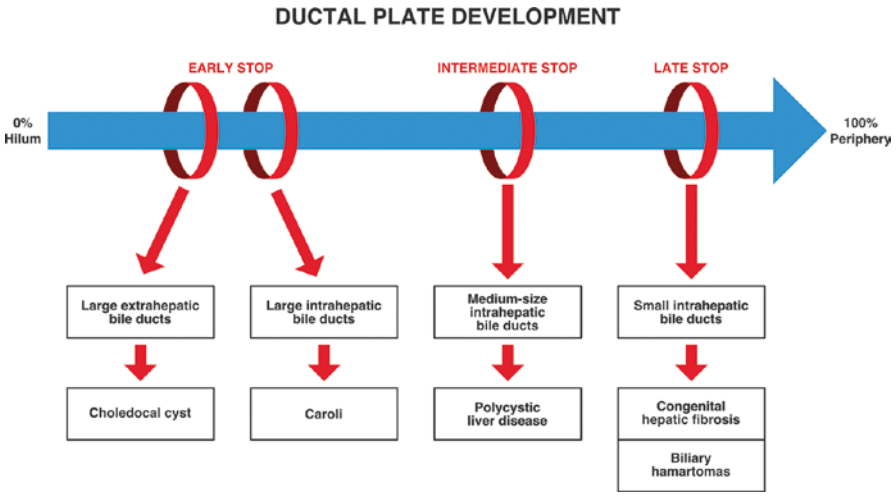

Fig. 5.1 Schematic representation of biliary system malformations. The remodeling and partial involution of the ductal plate starts at the hilum around the 12th week and progresses peripherally until it is completed by the end of the gestation. The phenotype of the fibro-polycystic liver disease depends on the stage of the embryological development in which the defect occurs

5.3 Clinical Characteristics

The onset of symptoms occurs during childhood or young adulthood, with intermittent abdominal pain (at the right upper quadrant), jaundice, and pruritus related to recurrent cholangitis episodes. Possible complications are related to bile stasis: intrahepatic stone formation, bacteremia, sepsis, hepatic abscesses, recurrent cholangitis, and secondary biliary cirrhosis. Cholangitis and abscesses are typically characterized by fever and malaise. An increased risk of cholangiocarcinoma is reported with a prevalence of 7%; chronic inflammation of the biliary epithelium may play an important role.

When both early and late stage anomalies of the ductal plate development occur, the CD coexists with another fibro-polycystic liver disease, typically congenital hepatic fibrosis. This condition is called Caroli's syndrome and it's more frequent than Caroli's disease. The association with congenital hepatic fibrosis can lead eventually to the development of portal hypertension, with subsequent ascites and variceal hemorrhages.

ARPKD and other fibro-polycystic liver diseases can occur in association with CD and congenital hepatic fibrosis.

5.4 Diagnosis

Imaging techniques well demonstrate diffuse, lobar, or segmental involvement of intrahepatic biliary ducts, as non-obstructive saccular or fusiform dilatations, usually up to about 5 cm in diameter, often containing calculi or sludge. Ultrasound (US) shows intraductal bridging, as echogenic septa traversing the dilated lumen, and stones, if present. The appearance of echogenic portal vein branches surrounded by hypoechoic dilated bile ducts is better seen on axial Computed Tomography (CT) scans examination as "central dot sign," in which the dot is represented by the portal branch cross-sectional view and become more evident after contrast media administration, in portal phase enhancement (Fig. 5.2). The "central dot sign" occasionally occurs in other pathologies (e.g., peribiliary cysts, periportal lymphedema, and jaundice due to biliary obstruction).

Magnetic Resonance Imaging (MRI) with cholangiopancreatography (MRCP) is the most efficient method to visualize non-invasively the biliary and pancreatic duct system. Dilated biliary tracts appear hypointense on T1-weighted images and hyperintense on T2w ones; signs of cholangitis (i.e., thickening of the walls with irregular margins and enhancement, due to fibrosis and edema) can also be recognized; furthermore, MRCP well demonstrates the associated stenoses (Fig. 5.3) and the continuity between cystic dilatations and the biliary tree. The T1-weighted images acquired after contrast media administration may reveal the "central dot sign" (Fig. 5.4), whereas the administration of hepatobiliary contrast agent (gadoxetic acid) may also prove communication of the cystic dilatations with the biliary tree (Fig. 5.5).

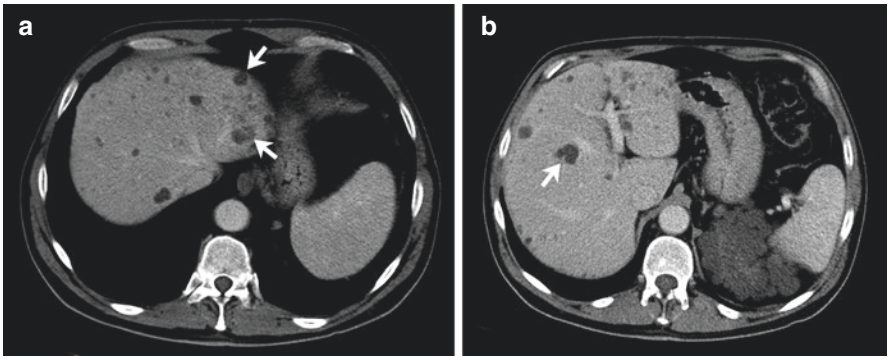

Fig. 5.2 Transverse CT scans obtained after contrast media injection in portal phase (**a**, **b**) showing multiple hypoattenuating liver lesions of different sizes scattered throughout the parenchyma. Some of them have a central hyperattenuating small vessel that creates the "central dot sign" (arrows). If the vessel is parallel to the plane of the image, the dot becomes a line

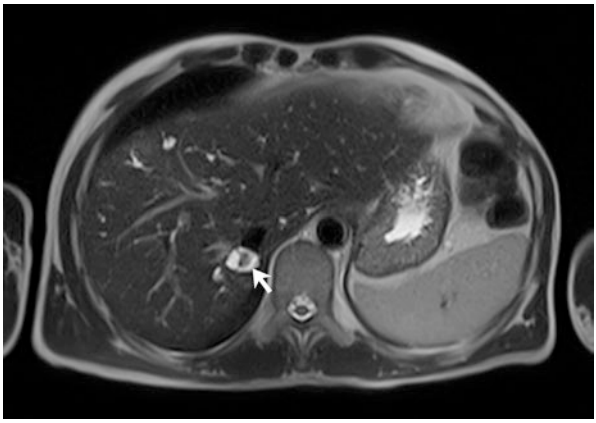

Fig. 5.3 Magnetic resonance T2-weighted transverse image showing a hyperintense cystic dilatation of the biliary tree that contains an intrahepatic stone, seen as a darker formation inside it (arrow)

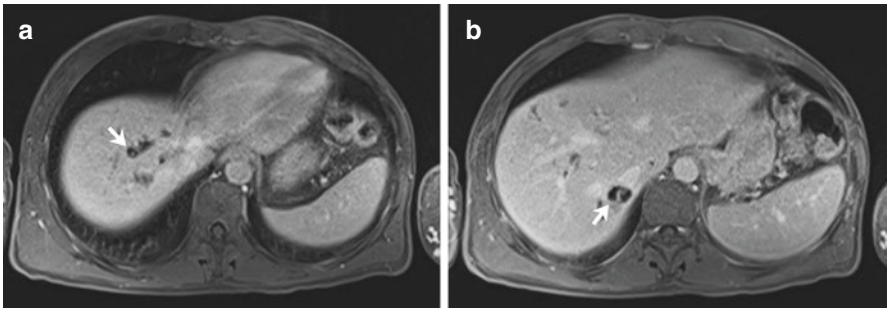

Fig. 5.4 Magnetic resonance T1-weighted transverse images after non-specific contrast agent injection: "central dot sign" due to the cross-sectional view of the vessel (arrow) (**a**); the vessel is parallel to the plane of the image, appearing as a line within the hypointense formation (**b**)

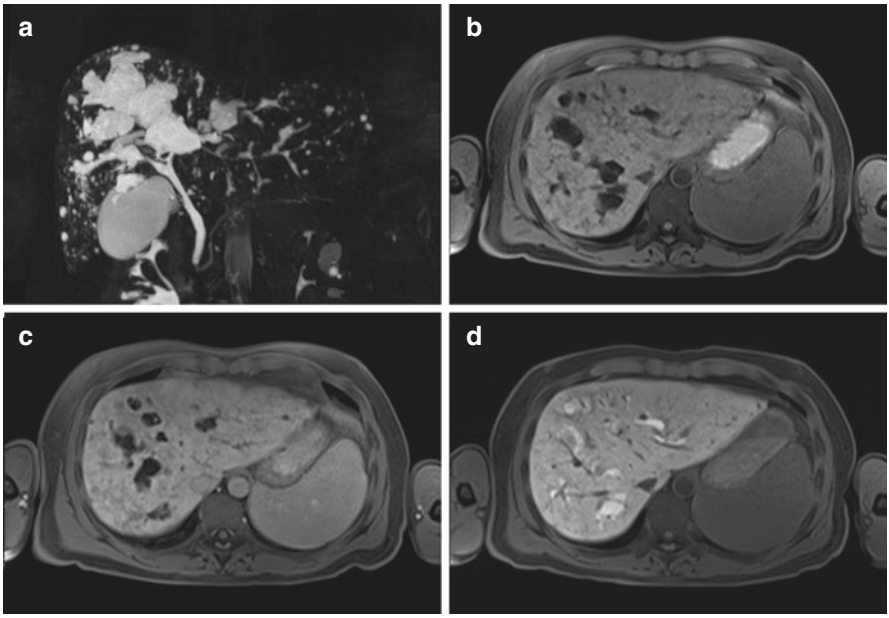

Fig. 5.5 T2-weighted MRCP image showing hyperintense cystic dilatation of the biliary tree (**a**). T1-weighted transverse images acquired before (**b**) and after the administration of hepatobiliary contrast agent (gadoxetic acid), depicting "central dot sign" in portal venous phase (**c**) and lumen contrast enhancement in hepatobiliary phase (**d**), confirming the communication of the cystic dilatations with the biliary tree

An older technique for confirmation of biliary dilatation is represented by the "HIDA scan," hepatic cholescintigraphy that uses radiotracers called TC^{99m}-IDA (iminodiacetic acid) analogs.

In case of hepatic abscess, a plain abdominal radiograph may show indirect signs like pneumobilia, gas beneath the diaphragm, and right-sided pleural effusion. US demonstrates poorly demarcated collections with variable appearance (i.e., hypo- to hyperechoic) and gas bubbles; no perfusion is observed in the central—necrotic—portion at Color Doppler. Contrast enhancement of the walls may be useful to measure the size of the lesion and to depict internal septation. Similarly, at CT scan "double target sign" is observed, with central low attenuation, a high attenuation inner rim (i.e., abscess membrane) that enhances early, and a low attenuation outer ring (i.e., parenchymal edema) that enhances on delayed phase. MRI identifies centrally hypointense lesions on T1-weighted and hyperintense signal on T2-weighted images, with enhancement of the capsule and septations, and signal restriction on diffusion weighted images (DWI).

The association between CD and cholangiocarcinoma requires a regular follow-up, usually performed with CT or MR (Fig. 5.6).

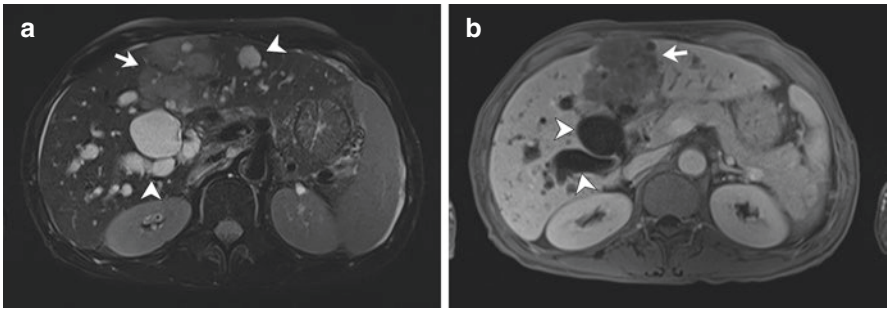

Fig. 5.6 Magnetic resonance of a patient with Caroli's disease who developed an intrahepatic cholangiocarcinoma. T2-weighted (**a**) and T1-weighted (**b**) transverse images showing an irregular mass slightly hyperintense in T2, with poor and inhomogeneous contrast enhancement in T1 that turned out to be a cholangiocarcinoma (arrow). It compressed the biliary tree, causing dilation of the biliary tree, that coexisted with the dilation caused by CD

5.5 Differential Diagnosis

Differential diagnosis includes most of the other fibro-polycystic diseases, primary sclerosing cholangitis, pyogenic cholangitis, and obstructive biliary dilatation.

- *Polycystic liver disease*: hereditary condition that occur in up to 90% of patients with *autosomal dominant polycystic kidney disease*. No biliary duct dilatation or communication with biliary ducts are generally observed. They are usually more numerous and may bleed, causing a fluid-fluid level inside.
- *Primary sclerosing cholangitis*: inflammatory condition associated with *inflammatory bowel disease* in 70% of patients. Dilatations are typically smaller, fusiform and paired with strictures resulting in a "beaded appearance" of the biliary tree. Suggestive hepatic morphology changes are enlargement of the caudate and left lobe hypertrophy. If elevated serum IgG-4 is found along with other IgG-4 related conditions, an IgG-4 related sclerosing cholangitis should be considered.
- *Pyogenic cholangitis*: should be suspected in patients with fever and septicemia. Imaging demonstrates biliary strictures and dilatations of both intra- and extrahepatic bile ducts that usually contain stones.
- *Obstructive biliary dilatation*: a mechanical obstruction of the biliary tree is demonstrated.

CD can coexist with *other fibro-polycystic liver disease*, such as biliary hamartomas (Fig. 5.7).

Fig. 5.7 The same patient of Fig. 5.2 underwent MRCP, for further evaluation, showing the cystic dilatation of the biliary tree already depicted by CT and multiple small hyperintense lesions scattered throughout the liver without communication with the biliary tree, pathognomonic of biliary hamartomas. CD coexists with biliary hamartomas

5.6 Treatment

If CD is not diffuse, segmentectomy or lobectomy may be performed; otherwise, conservative management is generally applied (i.e., ursodeoxycholic acid), and liver transplantation could be considered. For cholangitis and hepatic abscesses, antibiotic therapy is required. Interventional radiology percutaneous drainage, under US or CT guidance, plays a role for bigger abscess, if no septations are present [1–27].

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