Fibropolycystic Liver Diseases

Carlos Bilreiro and Inês Santiago

Contents

C. Bilreiro
PreClinical MRI Lab, Champalimaud Foundation, Lisbon, Portugal

I. Santiago (✉)
PreClinical MRI Lab, Champalimaud Foundation, Lisbon, Portugal

Radiology Department, Champalimaud Foundation, Aveiro, Portugal

Nova Medical School, Lisbon, Portugal

Abstract

Fibropolycystic liver diseases are a group of congenital disorders with a common origin in ductal plate developmental abnormalities and varied fenotypes. They include the simple hepatic cysts, Caroli disease and syndrome, polycystic liver diseases, congenital hepatic fibrosis and biliary hamartomas. In this chapter, we first discuss the embryologic develo-

E. Quaia (ed.), *Imaging of the Liver and Intra-hepatic Biliary Tract*,
Medical Radiology, Diagnostic Imaging, https://doi.org/10.1007/978-3-030-38983-3_11

pent of the normal ductal plate and of the multiple ductal plate abnormalities. Then, we individually address the various fibropolycystic liver diseases with respect to their epidemiology, clinical features and therapeutic management, with a special emphasis on the description and illustration of their imaging findings.

1 Clinical Background

Fibropolycystic liver diseases represent a heterogeneous group of disorders, with a common origin in ductal plate development anomalies. These include the simple hepatic cysts, Caroli disease and syndrome, polycystic liver diseases, congenital hepatic fibrosis (CHF) and biliary hamartomas (von Meyenburg complexes).

1.1 Embryology: The Ductal Plate

During the fourth gestational week, the hepatic diverticulum arises from the ventral wall of the primitive midgut (Fig. 1a) (Ando 2010). This diverticulum then develops a cranially located pars hepatica, which originates in the liver primordium and the common hepatic duct. Caudally, a superior and an inferior bud also develops (Fig. 1b). The superior bud originates in the gallbladder and cystic and choledochal ducts, while the inferior bud originates in the ventral portion of the pancreas (Fig. 1c–e). The choledochal duct and ventral portion of the pancreas then rotate 180° and, by the sixth gestational week, reach their definitive location (Fig. 1f).

The ductal plate is formed in the eighth gestational week, originating from hepatoblasts in the liver primordium (Crawford 2002). These become

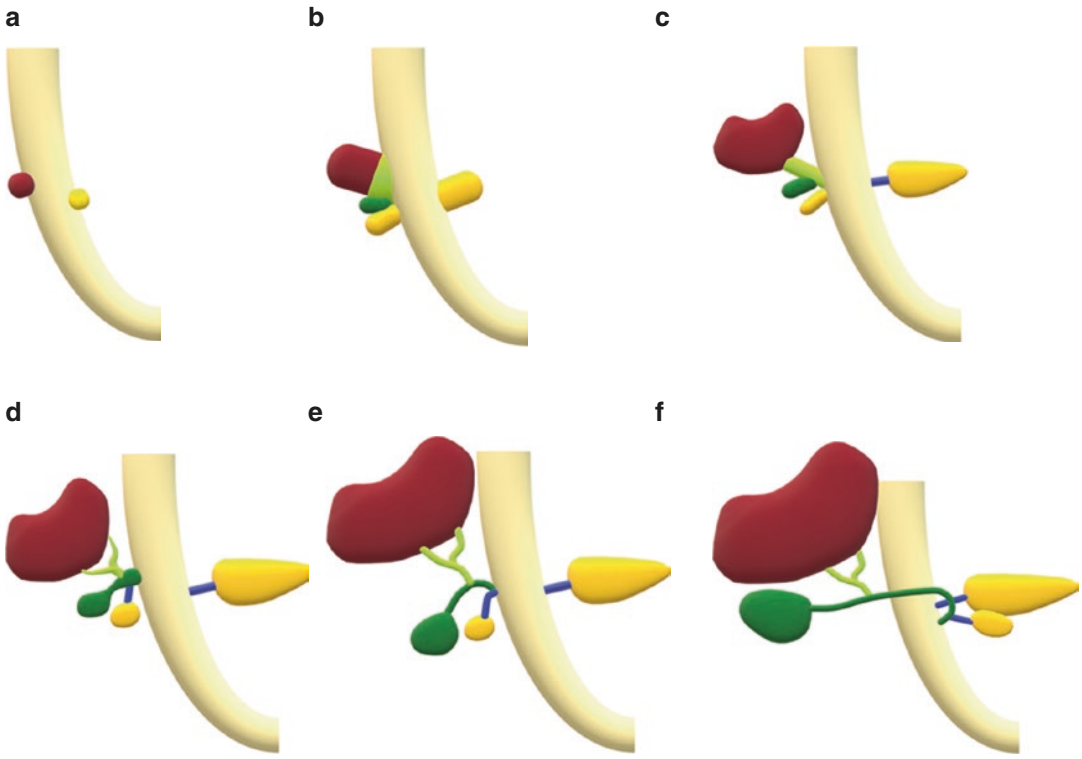

Fig. 1 Schematic representation of liver, pancreas, gallbladder, and biliary tree embryologic development from weeks 4 to 6, in chronological order from (**a**–**f**)

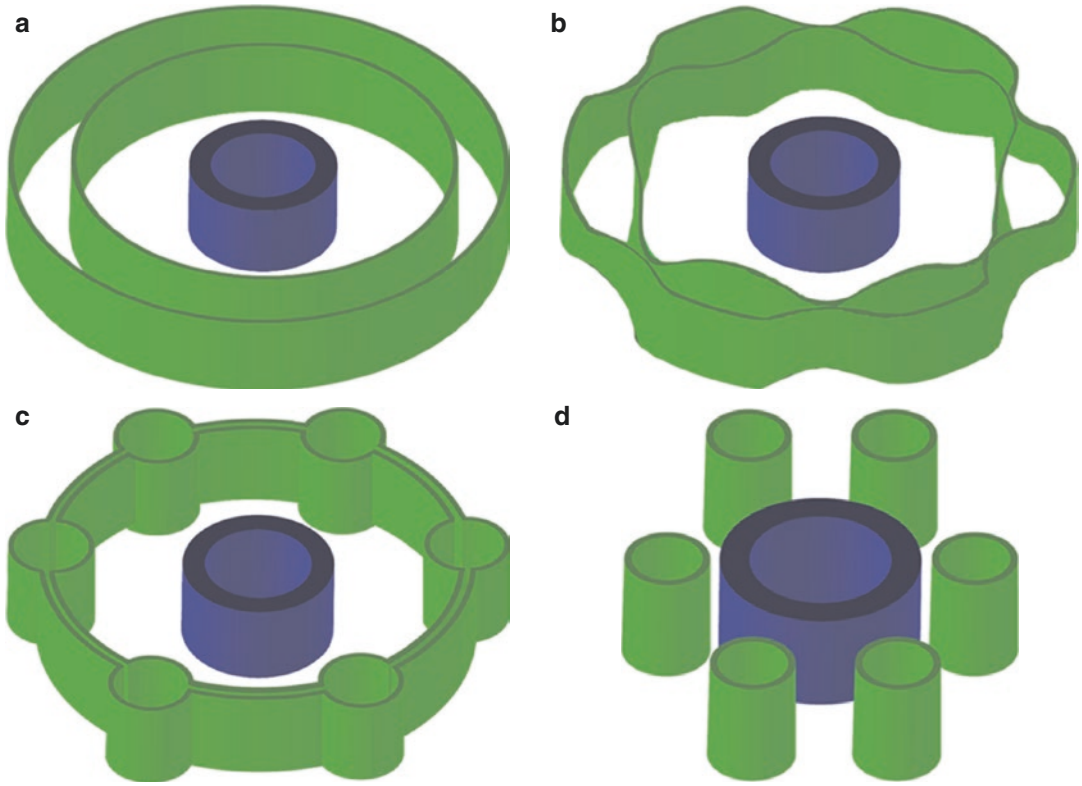

Fig. 2 Schematic representation of the ductal plate development, in chronological order from (**a**–**d**)

epithelial cells arranged in double-layer cylindrical structures, adjacent to the mesenchyme of portal vein branches (Fig. 2a). This process begins in the hepatic hilum and progresses in a centrifugal fashion to the liver periphery. Between the 11th and 13th weeks of gestation, the ductal plate begins a remodeling process, in which the ductal plates separate by apoptotic deletion of intervening cells and create progressively cylindrical structures (Fig. 2b, c). These structures then mature into a network of longitudinally arranged bile ducts, up until the postnatal period (Fig. 2d) (Crawford 2002; Lazaridis et al. 2004).

1.2 Development of Fibropolycystic Liver Diseases

Developmental disorders of the ductal plate are responsible for fibropolycystic liver diseases, as represented in Fig. 3. Depending on the anatomic site and caliber of branching duct disorder, different pathological entities may occur (Brancatelli et al. 2005; Santiago et al. 2012). Malformations of the larger extrahepatic bile ducts may create choledochal cysts (not reviewed in this chapter). Caroli disease is caused by large intrahepatic duct developmental abnormalities. Biliary atresia, not reviewed in this chapter, refers to underdevelopment of large intrahepatic and extrahepatic bile ducts. When medium-sized intrahepatic ducts are affected, polycystic liver disease may ensue. The malformation of smaller caliber intrahepatic ducts may cause CHF and biliary hamartomas (von Meyenburg complexes).

The pathological entities in this spectrum may occur simultaneously and in association with a common genetic background. Most frequently, ADPKD and ARPKD, with genetic defects in PKD1, PKD2, and PKHD1, respectively, may associate with polycystic liver disease, CHF, Caroli disease, and biliary hamartomas (Dell

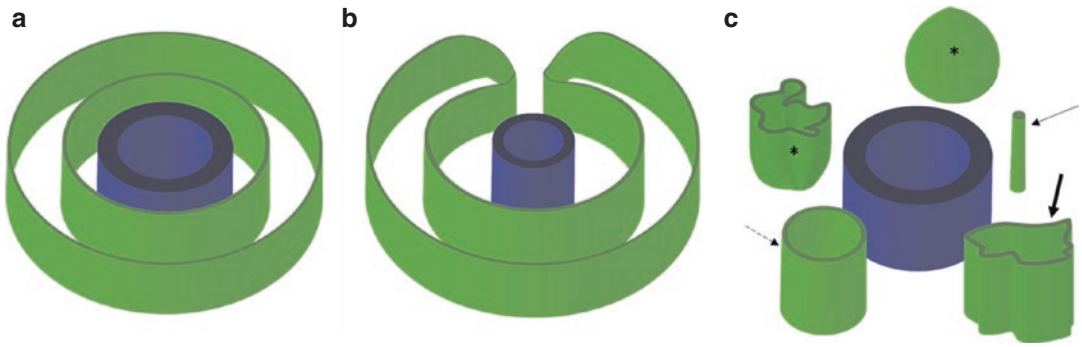

Fig. 3 Schematic representation of ductal plate development malformations. When development is arrested in the early gestational period, large-sized intrahepatic bile ducts are affected and saccular/fusiform dilatations of the biliary tree will be found in the adult (**a**). These may be pierced by portal mesenchyma, the latter usually containing an abnormally small portal venous branch, as observed in Caroli disease (**b**). An arrest in ductal plate formation occurring later in embryonic development will affect smaller ducts and may originate in abnormally thin or even obliterated ducts (thin arrows in **c**) as in congenital hepatic fibrosis, simple cysts (* in **c**) as in ADPKD and ADPLD, or biliary hamartomas (thick arrows in **c**)

2011; Mehta and Jim 2017). Also, Caroli syndrome refers to the presence of Caroli disease occurring simultaneously with CHF (both intrahepatic large- and small-caliber bile ducts are affected). Several other associations between congenital kidney diseases and ductal plate developmental anomalies have been described, mainly with CHF, including nephronophthisis type 3, Jeune syndrome, Joubert syndrome, Meckel syndrome, Bardet–Biedl syndrome, oral-facial-digital syndrome type 1, and Ivemark syndrome (Gunay-Aygun et al. 2008). Also, an isolated form of polycystic liver disease may occur (autosomal dominant polycystic liver disease—ADPLD), without kidney abnormalities, due to genetic defects in PRKCSH, SEC36, LRP5, and recently identified SEC61B and ALG8 (Drenth et al. 2004; Cnossen et al. 2014; Besse et al. 2017; van de Laarschot and Drenth 2018).

2 Simple Hepatic Cyst

2.1 Epidemiology, Clinical Features, and Management

The simple hepatic cyst is a benign cyst, lined by simple cuboidal or columnar biliary-type epithelium. It is a very common lesion, the second most common benign liver lesion in adults after hepatic hemangioma, with increasing prevalence in advancing age (van de Laarschot and Drenth 2018; Gaines and Sampson 1989). It is usually an incidental finding in imaging studies, without clinical manifestations. Rarely, patients might present with symptoms due to compression of adjacent structures, infection (Fig. 4e–h), hemorrhage, or rupture (Sayma et al. 2019; Yoshida et al. 2003). Simple hepatic cysts follow an invariably benign course and intervention is only needed in rare symptomatic cases or when the diagnosis is uncertain (Rogers et al. 2007).

2.2 Imaging Findings

In imaging studies, the diagnosis of simple hepatic cyst is usually straightforward (Fig. 4). In ultrasound imaging, it most frequently presents as a well-defined anechoic lesion, sometimes with lobulated contours (Gaines and Sampson 1989). Posterior acoustic enhancement might be seen, if the lesion is large enough. Fine septa in its interior might be observed, but without solid components or vascularization when using Doppler ultrasound. Simple hepatic cysts present as well-defined water density lesions in CT scans (Horton et al. 1999). In MRI, these appear as well-defined lesions, with homogeneous high signal intensity on T2- and low signal intensity

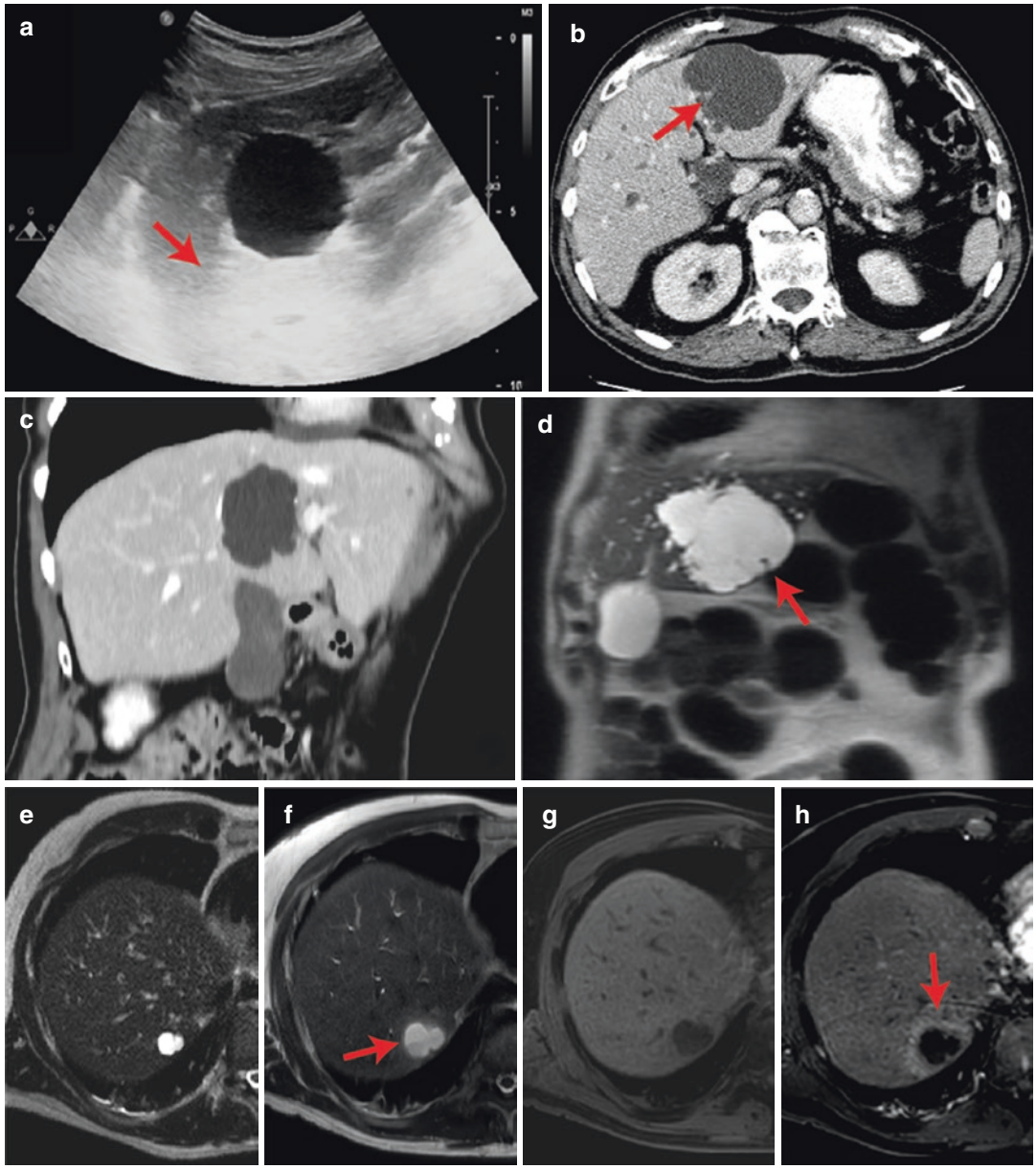

Fig. 4 Simple hepatic cysts are typically homogeneous and well-defined anechoic (**a**), hypoattenuating (**b** and **c**), and strongly T2 hyperintense lesions (**d** and **e**) on ultrasound, CT, and MR imaging, respectively. They typically exhibit posterior acoustic enhancement on ultrasound (arrow in **a**). Although more frequently round (**a**), they may also be lobulated (**b**, **e**) and sometimes present with thin regular septa (arrows in **b** and **d**), which should not enhance after IV contrast administration. An unusual complication of simple hepatic cysts is infection, which may present with an increase in cyst size (**f** vs. **e**), heterogeneous content sometimes with air-fluid or fluid-fluid levels (arrow in **f**), and contour blurring (**f**) with peripheral arterial hyperenhancement (**h** vs. **g**)

on T1-weighted images. There should be no enhancement of internal components after intravenous contrast administration in both CT and MRI (Horton et al. 1999; Elsayes et al. 2005). If enhancing internal components are seen, cystadenoma or cystadenocarcinoma should be the main diagnostic possibilities, when considering a primary liver lesion.

3 Caroli Disease and Syndrome

3.1 Epidemiology, Clinical Features, and Management

Caroli first described two forms of disease in the spectrum of the ductal plate malformations (Caroli et al. 1958). These became known as Caroli syndrome and Caroli disease. Both diseases affect the large-caliber intrahepatic bile ducts and Caroli syndrome also affects the small-caliber intrahepatic bile ducts, occurring with simultaneous CHF. Both are inherited in an autosomal recessive fashion and can be associated with ARPKD or ADPKD (Jordon et al. 1989). Abnormal ductal plate remodeling with persistence of dilated ductal plate remnants is thought to be the cause for Caroli disease (Fig. 3b) (Desmet 2005).

Patients with Caroli disease and syndrome might present with abdominal pain, enlarged liver, and recurrent episodes of cholangitis. Because Caroli syndrome is associated with CHF, these patients might present with signs of portal hypertension. As both diseases occur with cholestasis, intrahepatic sludge and stone formation are common. This also puts patients at a higher risk for developing cholangiocarcinoma (Bloustein 1977). The prognosis for both conditions is relatively poor, with frequent secondary biliary cirrhosis. Therapy mainly consists of antibiotics when acute cholangitis occurs; drainage procedures might be performed when there are liver abscesses. Liver transplantation is an important therapeutic option and, if the disease affects predominantly one liver lobe, partial hepatectomy might be performed with success (Ramond et al. 1984; Lendoire et al. 2011; Lendoire et al. 2007; Kassahun et al. 2005).

3.2 Imaging Findings

Typical imaging findings in Caroli disease include saccular and/or fusiform dilatation of intrahepatic bile ducts (Fig. 5a, b), often containing biliary sludge and stones (Brancatelli et al. 2005; Santiago et al. 2012; Mamone et al. 2019). A classical finding is the "central dot sign" in CT and MRI studies (Fig. 6), which represents the central vascular bundle surrounded by the dilated biliary duct. The main differential diagnosis is with polycystic liver disease, which can be difficult. MRCP may help in this regard, when it shows communication of the intrahepatic bile ducts with the liver cysts (Fig. 5b). Another finding used to demonstrate communication with the biliary tree and perform this differential diagnosis is the presence of intracystic gadolinium, when performing MRI with intracellular hepatospecific contrast agents that undergo uptake by hepatocytes and are later secreted into the bile ducts, during the hepatobiliary phase (Fig. 5c–e) (Brancatelli et al. 2005; Santiago et al. 2012; Mamone et al. 2019; Lewis et al. 2016). The most used contrast agents in this regard are gadoxetic acid (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA) (Lewis et al. 2016).

4 Polycystic Liver Disease

4.1 Epidemiology, Clinical Features, and Management

Polycystic liver diseases are characterized by the growth of multiple cysts in the liver, without communication to the biliary tree. These cysts are lined by functional biliary epithelium and usually grow progressively in size, ultimately replacing a significant portion of the liver parenchyma. These may occur in association with ADPKD and ARPKD, or in isolation as an autosomal dominant polycystic liver disease (ADPLD) (Cnossen and Drenth 2014). The most common of these disorders is ADPKD, with estimated prevalence ranging from 1:400 to 1:4033 births; a more recent review reports a prevalence of near 4:10,000 (or 1:2500) (Perugorria et al. 2014; Torres et al. 2007; Willey et al. 2017). ARPKD is significantly less common, with an estimated prevalence of 1:20,000 births and a high mortality rate shortly after birth; approximately half of newborns die of pulmonary complications (Perugorria et al. 2014; Torres et al. 2007; Zerres et al. 1998; Paul and VandenHeuvel 2014).

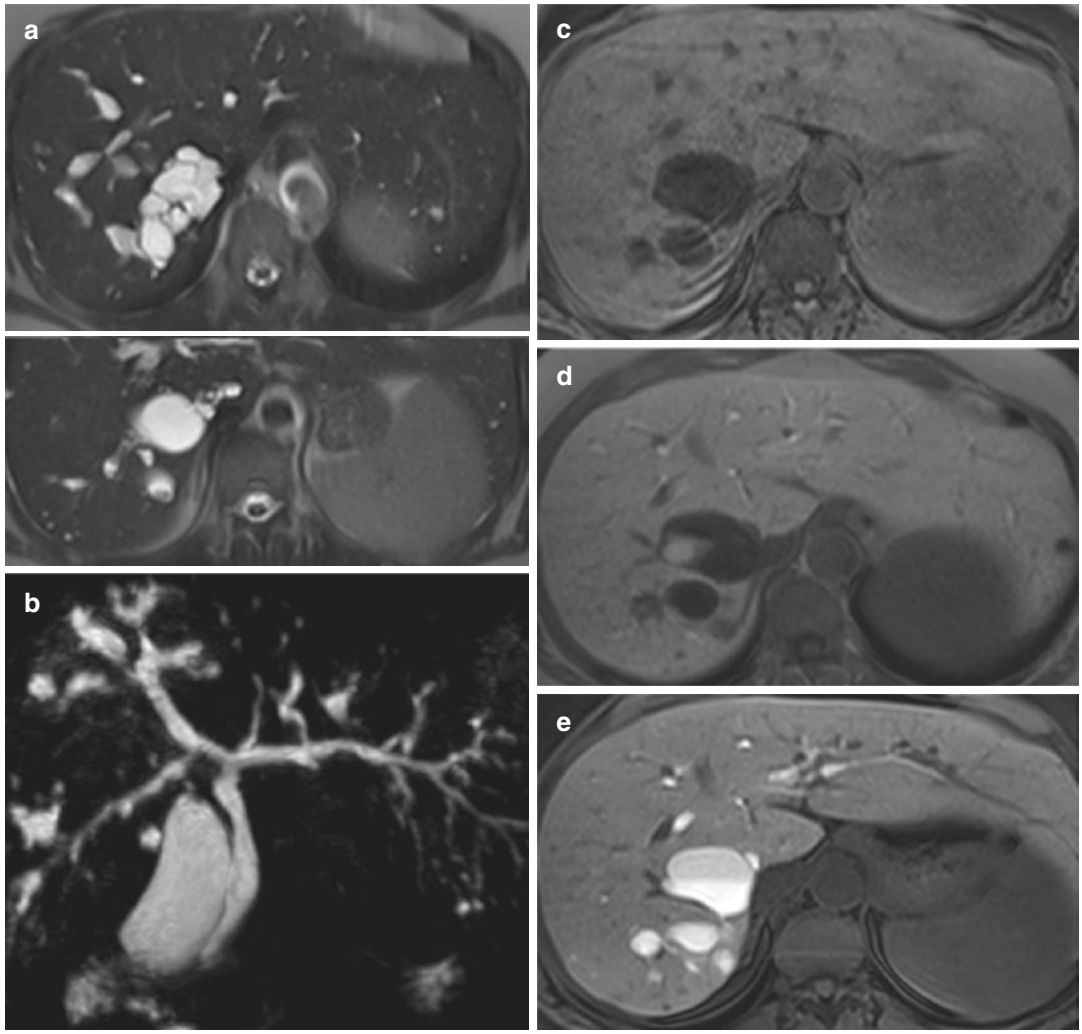

Fig. 5 Caroli disease presenting with lobulated cystic lesions predominantly located in the posterior sector of the right liver lobe (**a**) corresponding to saccular focal dilatations of the biliary tree (**b**). After Gd-EOB-DTPA administration, a progressive but slow filling of the cystic lesions on the hepatobiliary phase is observed, proving communication with the biliary tree (**c**: pre-contrast; **d**: post-contrast at 10 min; **e**: post-contrast at 3 h)

ADPLD is the rarest form of these diseases, with an estimated prevalence of 1:100,000 (Perugorria et al. 2014).

Several germline mutations have been identified in the development of these diseases. ADPKD and ARPKD are associated with germline mutations in PKD1, PKD2 and PKHD1, respectively, while ADPLD has been associated with mutations in PRKCSH, SEC63, LRP5, ALG8, and SEC61 (Drenth et al. 2004; Cnossen et al. 2014; Besse et al. 2017; van de Laarschot and Drenth 2018).

ADPKD usually manifests clinically in adulthood. Hypertension, hematuria, proteinuria, and recurrent pyelonephritis may dominate the initial presentation. A progression to end-stage chronic kidney disease occurs in approximately 45% of patients by the age of 60 years (Gabow 1993). The hallmark of this condition is the presence of renal cysts, affecting virtually all patients as age advances. The presence of liver cysts affects 30–70% of patients, more frequently women, possibly due to hormonal influences (Mamone et al. 2019). Treatment directed to liver cysts may

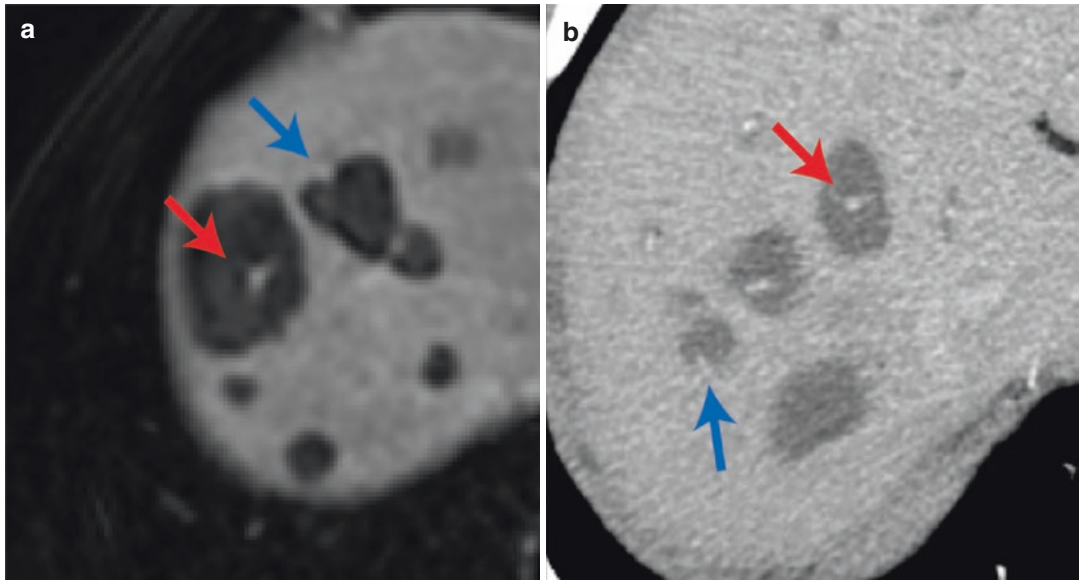

Fig. 6 Central dot sign. Two cases of Caroli disease exhibiting the characteristic central dot sign on post-contrast portal venous phase imaging are depicted, on MR (**a**) and CT (**b**). The central dot sign (red arrows) results from the piercing of the ectatic abnormal bile duct by the portal sheet. When it contains a portal venous branch, it is usually reduced in caliber, but the portal venous branch(es) may also be located at the periphery of the abnormal bile duct (blue arrows)

be necessary when there are complications: hemorrhage, infection, or compression of adjacent structures. Cyst drainage and antibiotics are the main therapeutic options when recurrent cyst infection occurs (Torres et al. 2007). New therapeutic options have emerged, and somatostatin analogue administration, namely lanreotide and octreotide, has shown efficacy in decreasing liver and kidney volume (van Keimpema et al. 2009; Hogan et al. 2010; Gevers et al. 2015). However, a recent trial concluded that lanreotide administration in late stages does not improve renal function and cannot be recommended for this specific purpose (Meijer et al. 2018).

ARPKD, on the other hand, manifests early in infancy and childhood, with strikingly enlarged kidneys with innumerable tiny cysts (Drenth et al. 2010). These abnormalities are nowadays frequently found during gestational ultrasound, sometimes with Potter syndrome (oligohydramnios with enlarged kidneys, pulmonary hypoplasia, characteristic facies, and contracted limbs with clubfeet). This condition has approximately 50% mortality rate in the neonatal period, and the children that survive early infancy present later with hypertension, frequently requiring multidrug therapy (Bergmann et al. 2005). Also in later stages, children may present with dominant hepatobiliary clinical findings. The liver involvement is similar to CHF, with hepatic fibrosis and hyperplastic biliary ducts (Turkbey et al. 2009). Although liver function is frequently preserved until late stages, progressive hepatic fibrosis and portal hypertension ultimately lead to the development of esophageal varices with upper gastrointestinal bleeding and hypersplenism with pancytopenia (Drenth et al. 2010; Guay-Woodford and Desmond 2003). A combined liver-kidney transplant is usually considered early in the course of the disease. Caroli disease may be associated with ARPKD; therapeutic options due to hepatic cyst complications or liver function decline are similar as explained previously, namely cyst drainage, antibiotics, partial hepatectomy, and liver transplant.

ADPLD has a milder clinical course, unassociated with significant kidney disease. Renal cysts may occur, but as a mild sporadic finding when compared with ADPKD or ARPKD and without decrease in renal function (Mamone et al. 2019). Arbitrarily, the diagnosis can be made when there are more than 20 liver cysts, or more than 4 when there is a family history of ADPLD (van Keimpema et al. 2009). Patients are frequently asymptomatic until late adulthood. Symptoms may arise from compression of abdominal structures due to large cysts, cyst infection, hemorrhage, or rupture. Therapeutic intervention might be necessary in symptomatic patients; cyst aspiration, sclerotherapy, partial hepatectomy, or even liver transplantation can be considered (van Keimpema et al. 2008; Russell and Pinson 2007; Neijenhuis et al. 2019). Similar to ADPKD, the administration of somatostatin analogues has shown promise in reducing liver volume in ADPLD (van Keimpema et al. 2009; Hogan et al. 2010; Gevers et al. 2015).

4.2 Imaging Findings

Regarding imaging findings of each of these polycystic liver diseases, ADPKD and ADPLD may have similar hepatic features with liver enlargement and multiple cysts; however the major involvement of kidneys in ADPKD will help in the differential diagnosis (Fig. 7a, b). The size of cysts can vary from 1 mm to 12 cm (Brancatelli et al. 2005; Morgan et al. 2006). The hepatic cysts have similar imaging characteristics as simple cysts, presenting in ultrasound as well-defined anechoic lesions and in CT as well-defined water density lesions. In MRI, the multiple cysts are also seen with high signal intensity in T2-weighted images and low signal intensity in T1-weighted images. Complicated cysts appear with heterogeneous content in ultrasound, higher density in CT scans, and heterogeneous signal in MRI (high T1 signal intensity if hemorrhage is present) (Fig. 7c). A previously complicated cyst can develop peripheral calcifications (Santiago et al. 2012; Mamone et al.

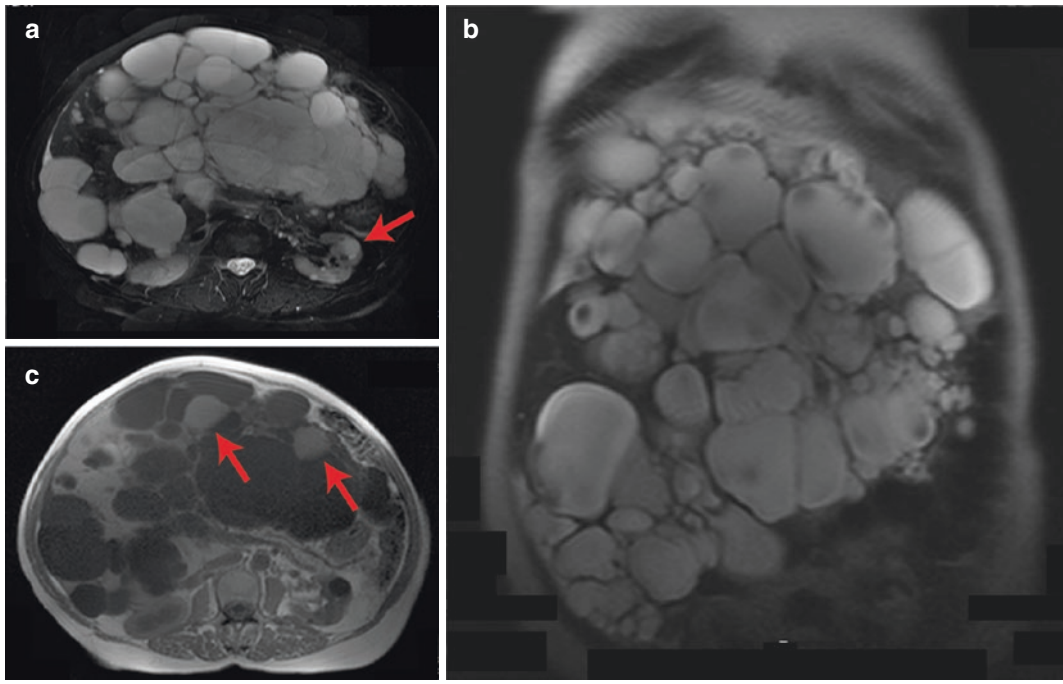

Fig. 7 Autosomal dominant polycystic liver disease. Numerous T2-hyperintense liver cysts of various sizes are depicted (**a**), causing massive hepatomegaly (**b**). Notice how the left kidney is relatively spared (arrow in **a**). Some cysts exhibit T1 hyperintensity (arrows in **c**) likely due to previous hemorrhage

2019). To perform the differential diagnosis with Caroli disease, MRCP and hepatospecific contrast-enhanced MRI have specific findings in this regard, as previously mentioned, with both modalities showing absence of communication of hepatic cysts with the biliary tree in ADPLD and ADPKD (Brancatelli et al. 2005; Santiago et al. 2012; Mamone et al. 2019). Also, peribiliary cysts have been associated with ADPLD and ADPKD (Mamone et al. 2019; Lewis et al. 2016). These are usually smaller than 10 mm and may present as a discrete string of cysts or tubular structures, developing within the periductal connective tissue. These also do not communicate with the biliary tree; however, they may cause biliary obstruction.

Imaging findings of ARPKD differ, however, as these are similar with CHF. Periportal fibrosis, irregular dilatation of the biliary tree, regenerative nodules, and a coarse liver texture may be observed (Lonergan et al. 2000). Portal hypertension eventually develops and imaging findings reflect this, with splenomegaly and venous collateral development with esophageal varices. Ultrasound may show the coarse liver texture, with echogenic portal tracts thought to represent periportal fibrosis. CT and MRI also depict these same findings, with better identification of regenerative nodules and findings related to portal hypertension. MRCP may accurately depict the intrahepatic bile ducts' irregular caliber (Jung et al. 1999).

5 Congenital Hepatic Fibrosis

5.1 Epidemiology, Clinical Features, and Management

In contrast to the majority of previously discussed disorders, where hepatic or renal cysts were a dominant finding, CHF is mainly characterized by the presence of periportal fibrosis and irregular-caliber bile ducts (Desmet 1992; Venkatanarasimha et al. 2011). Typically, CHF has been associated with ARPKD, representing different manifestations of a spectrum of diseases (Desmet 1992). However, CHF can also present as an isolated condition or in the context of Caroli syndrome. A literature review reported 64% of CHF to appear associated with ARPKD, 25.6% associated with Caroli syndrome, and 9.5% in isolation (Srinath and Shneider 2012). Reports of association with ADPKD are rare (O'Brien et al. 2012).

Affected patients frequently maintain hepatocellular function until late stages of the disease (Mamone et al. 2019; Bergmann et al. 2005; Turkbey et al. 2009). Different forms of disease have been described: portal hypertensive, cholangitic, mixed, and latent (Desmet 1992; Venkatanarasimha et al. 2011). Portal hypertension can present in infancy and adulthood, with splenomegaly, hypersplenism, and pancytopenia as possible presenting features. Also, bleeding from gastroesophageal varices is a frequent presentation. Hepatopulmonary syndrome may present as an advanced finding. The pathogenesis of portal hypertension has been related to the compression of portal vein ramifications by periportal fibrosis and to abnormal development of portal vein branches, with hypoplastic small branches (Desmet 1992; Kerr et al. 1961). Patients with the cholangitic form of disease present mainly with cholestasis and recurrent episodes of cholangitis. As with other chronic cholestatic diseases, the risk for intrahepatic stones and cholangiocarcinoma development is increased (Summerfield et al. 1986). The mixed form of the disease represents simultaneous portal hypertensive and cholangitic findings; the latent form represents asymptomatic patients who are diagnosed incidentally during adulthood or later stages in life (Desmet 1992; Veigel et al. 2009).

Therapy is dependent on the manifestations of the disease. Variceal bleeding from portal hypertension can be treated with endoscopic procedures with sclerotherapy or ligation (Drenth et al. 2010; Shneider and Magid 2005). Elective surgical or percutaneous portosystemic shunt creation is an option in patients with gastroesophageal varices. Acute cholangitis can be treated with antibiotics and percutaneous procedures, if drainage is needed. Liver transplantation is also an option, mainly in patients with advanced hepatic disease or recurrent hemorrhagic or cholangitic complications (Shneider and Magid 2005). If Caroli syndrome is present, therapeutic interven-

tions directed to cyst complications may be needed, as explained previously in this chapter.

5.2 Imaging Findings

The imaging findings in CHF are generally not specific. Atrophy of the right liver lobe and hypertrophy of the lateral left and caudate lobes may be found, mimicking chronic liver disease from other causes (Santiago et al. 2012; Mamone et al. 2019). However, the left medial segments (IVa and IVb) may remain with normal volume, or be even enlarged (Zeitoun et al. 2004). The typical findings of portal hypertension, including portosystemic shunts (splenorenal and gastroesophageal, as the most typical), splenomegaly, and increased portal vein diameter, can be observed with ultrasound, CT, or MRI. The liver has a coarse texture in these imaging modalities. Periportal fibrosis can be identified as hyperechoic portal branches on ultrasound or high signal intensity in T2-weighted images along portal branches (Mamone et al. 2019; Veigel et al. 2009). Large regenerative hepatic nodules may appear in the course of portal hypertension; a hypervascular behavior due to increased arterial vascular supply has been demonstrated in contrast-enhanced studies (Brancatelli et al. 2005). These benign nodules are entirely similar to focal nodular hyperplasia in imaging studies. Vascular complications of portal hypertension can be initially assessed by ultrasound, and further identified on contrast-enhanced CT or MRI. MRCP can clearly depict the irregular caliber of intrahepatic bile ducts. In the presence of Caroli syndrome, the typical liver cysts will be a major imaging finding, as described previously.

6 Biliary Hamartomas (von Meyenburg Complexes)

6.1 Epidemiology, Clinical Features, and Management

Biliary hamartomas are clinically silent lesions, also known as von Meyenburg complexes, usually found incidentally in imaging studies (von Meyenburg 1918). These are dispersed throughout the liver parenchyma, as focal collections of dilated bile ducts, lined by biliary epithelium and surrounded by fibrous stroma (Mamone et al. 2019; Principe et al. 1997). The lesions are usually smaller than 10 mm and represent failure of involution of embryonic bile ducts, with a reported incidence of 5.6% in adult patients (Santiago et al. 2012; Zheng et al. 2005; Redston and Wanless 1996). The patients are asymptomatic and liver function is normal; direct complications of cystic lesions are not usual. However, reports of intrahepatic cholangiocarcinoma in patients with biliary hamartomas suggest an increased risk for the development of this tumor (Xu et al. 2009; Yang et al. 2017; Song et al. 2008; Jain et al. 2000).

6.2 Imaging Findings

As previously stated, these lesions are incidentally identified in imaging studies. In ultrasound studies, a typical presentation is with numerous hypoechoic or hyperechoic foci with comet-tail artifacts (Fig. 8a, b) (Santiago et al. 2012; Mamone et al. 2019; Zheng et al. 2005). On CT, the lesions are usually presented as disperse hypoattenuating foci (Fig. 8c, d) (Brancatelli et al. 2005). In MRI, the lesions are hyperintense in T2-weighted images (Fig. 8e) and hypointense in T1-weighted images. MRCP has a characteristic "starry-sky" appearance, with multiple foci of hyperintense cystic lesions dispersed throughout the liver parenchyma (Esseghaier et al. 2017; Giambelluca et al. 2018). The lesions do not enhance with the administration of intravenous contrast agents; however a peripheral rim enhancement has been described to represent compressed liver parenchyma (Semelka et al. 1999). As the cysts do not communicate with the biliary tree, they do not enhance in hepatobiliary phase of hepatospecific contrast agents. A differential diagnosis with multiple metastases may arise, and the characteristic findings of "starry sky" in MRCP (Fig. 8f) and comet-tail artifacts (arrow in Fig. 8b) in ultrasound help in this regard.

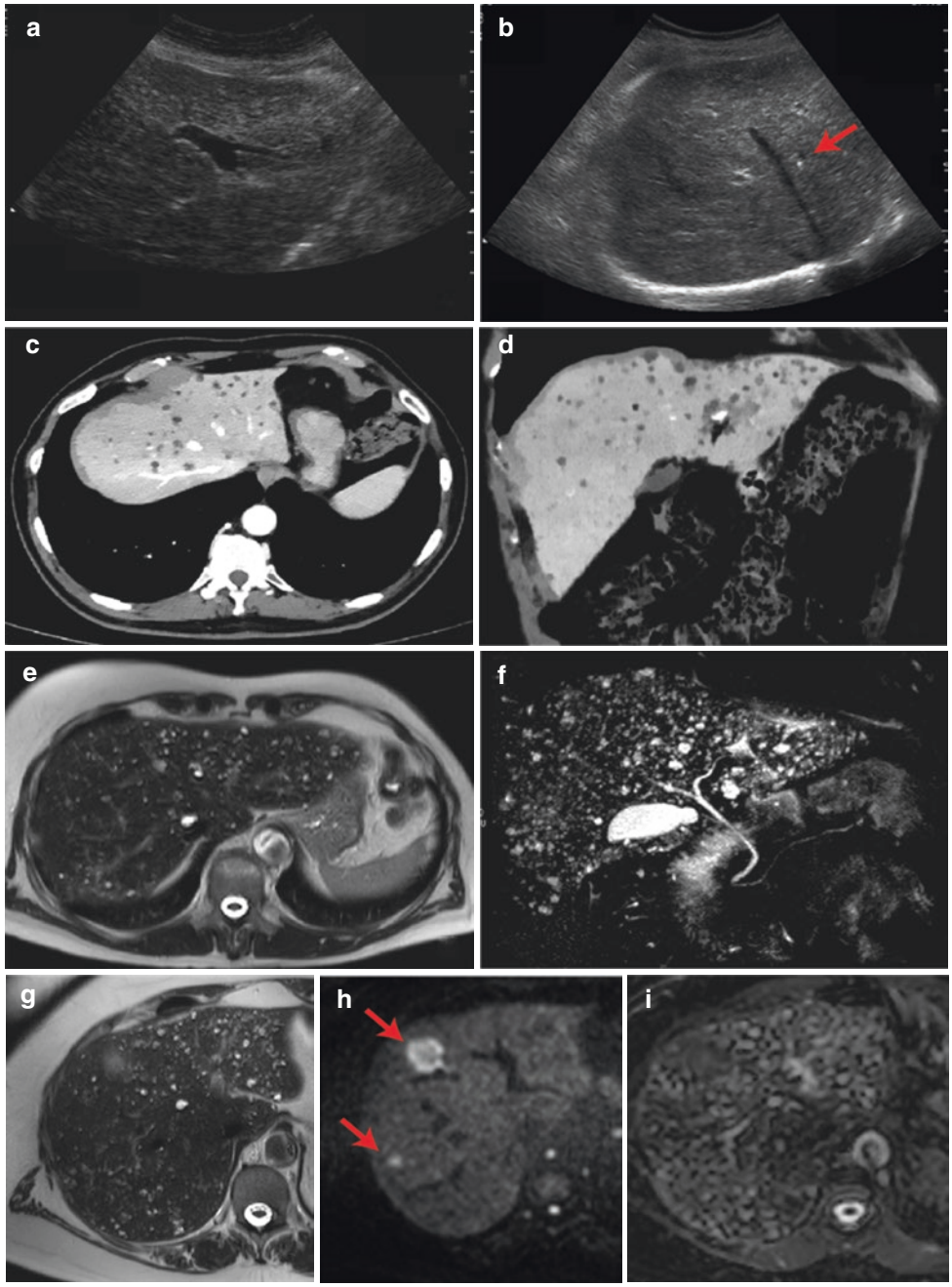

Fig. 8 Biliary hamartomas. Biliary hamartomas present on ultrasound as small (<15 mm) hyperechoic or anechoic lesions, depending on the amount of fluid content (**a**, **b**), sometimes with posterior acoustic enhancement causing the characteristic comet-tail artifact (arrow in **b**). On CT, they are usually hypoattenuating and non-enhancing (**c**: axial, portal venous phase post-contrast image; **d**: coronal oblique minimum intensity projection). The lesions are hyperintense on T2-weighted imaging (**e**) and particularly visible on heavily T2-weighted MRCP images, in which, when numerous, a "starry-sky" appearance is typical (**f**). Biliary hamartomas may obscure the detection of other liver lesions. In such cases, high b-value diffusion-weighted imaging may be particularly useful, highlighting solid, highly cellular, restricting lesions. (**g**–**i**) Depict a case of a patient with biliary hamartomas and two colorectal cancer liver metastases (arrows in **h**) as observed in T2-weighted imaging (**g**), b900 diffusion-weighted imaging (**h**), and corresponding ADC map (**i**)

7 Conclusion

The fibropolycystic liver diseases include several distinct pathological entities, with a common origin in developmental disorders of the ductal plate. Their management and therapeutic options are quite distinct; therefore a correct diagnosis must be performed. Imaging studies are critical in this regard and the findings described in this chapter represent the most important diagnostic features.

A short summary is present in Table 1.

Table 1 Key imaging findings diagnostic for each fibropolycystic liver disease

Fibropolycystic disease	Key imaging findings
Simple hepatic cyst	– Well-defined lesion, without solid or enhancing components – Anechoic in ultrasound – Water density in CT – Hyperintense in T2WI/hypointense in T1WI
Caroli disease and syndrome	– Saccular and fusiform dilatation of intrahepatic bile ducts – Intrahepatic biliary sludge and stones – Central dot sign in CT and MRI – Intracystic gadolinium with hepatospecific contrast agents
ADPLD	– No significant kidney disease – Liver enlargement – Multiple liver cysts with varying dimensions – Complicated cysts appear heterogeneous in ultrasound, high density in CT, and heterogeneous signal in MRI – Peripheral calcifications may appear in previously complicated cysts – Hepatospecific contrast agents show no intracystic gadolinium
ADPKD	– Kidney involvement with multiple cysts – Liver enlargement – Multiple liver cysts with varying dimensions – Complicated cysts appear heterogeneous in ultrasound, high density in CT, and heterogeneous signal in MRI – Peripheral calcifications may appear in previously complicated cysts – Hepatospecific contrast agents show no intracystic gadolinium
ARPKD	– Similar to CHF – Findings related to portal hypertension – Coarse liver texture – Portal tracts echogenic in ultrasound and hyperintense in T2WI – MRCP depicts the intrahepatic bile ducts' irregular caliber – Atrophy of the right liver lobe and hypertrophy of the lateral left and caudate with left medial segments with normal/enlarged volume – Large regenerative hepatic nodules
CHF	– Similar to ARPKD – Findings related to portal hypertension – Coarse liver texture – Portal tracts echogenic in ultrasound and hyperintense in T2WI MRI – MRCP depicts the intrahepatic bile ducts' irregular caliber – Atrophy of the right liver lobe and hypertrophy of the lateral left and caudate with left medial segments with normal/enlarged volume – Large regenerative hepatic nodules
Biliary hamartomas	– Ultrasound with hypo/hyperechoic foci with comet-tail artifacts – Hyperintense tiny foci in T2WI – MRCP with "starry-sky" appearance

References

Ando H (2010) Embryology of the biliary tract. Dig Surg 27:87–89

Bergmann C, Senderek J, Windelen E, Küpper F, Middeldorf I, Schneider F, Dornia C, Rudnik-Schöneborn S, Konrad M, Schmitt CP, Seeman T, Neuhaus TJ, Vester U, Kirfel J, Büttner R, Zerres K (2005) Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int 67: 829–848

Besse W, Dong K, Choi J, Punia S, Fedeles SV, Choi M, Gallagher AR, Huang EB, Gulati A, Knight J, Mane S, Tahvanainen E, Tahvanainen P, Sanna-Cherchi S, Lifton RP, Watnick T, Pei YP, Torres VE, Somlo S (2017) Isolated polycystic liver disease genes define effectors of polycystin-1 function. J Clin Invest 127:3558

Bloustein PA (1977) Association of carcinoma with congenital cystic conditions of the liver and bile ducts. Am J Gastroenterol 67:40–46

Brancatelli G, Federle MP, Vilgrain V, Vullierme MP, Marin D, Lagalla R (2005) Fibropolycystic liver disease: CT and MR imaging findings. Radiographics 25:659–670

Caroli J, Couinaud C, Soupault R et al (1958) Une affection nouvelle, sans doutecongénitale, des voies-biliaires: la dilatation cystiqueunilobaire des canaux-hépatiques. Sem Hop Paris 34:136–142

Cnossen WR, Drenth JP (2014) Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. Orphanet J Rare Dis 9:69

Cnossen WR, teMorsche RH, Hoischen A, Gilissen C, Chrispijn M, Venselaar H, Mehdi S, Bergmann C, Veltman JA, Drenth JP (2014) Whole-exome sequencing reveals LRP5 mutations and canonical Wnt signaling associated with hepatic cystogenesis. Proc Natl Acad Sci U S A 111:5343–5348

Crawford JM (2002) Development of the intrahepatic biliary tree. Semin Liver Dis 22:213–226

Dell KM (2011) The spectrum of polycystic kidney disease in children. Adv Chronic Kidney Dis 18: 339–347

Desmet VJ (1992) What is congenital hepatic fibrosis? Histopathology 20:465–477

Desmet VJ (2005) Cystic diseases of the liver: from embryology to malformations. Gastroenterol Clin Biol 9:858–860

Drenth JP, Chrispijn M, Bergmann C (2010) Congenital fibrocystic liver diseases. Best Pract Res Clin Gastroenterol 24:573–584

Drenth JP, Tahvanainen E, teMorsche RH, Tahvanainen P, Kääriäinen H, Höckerstedt K, van de Kamp JM, Breuning MH, Jansen JB (2004) Abnormal hepatocystin caused by truncating PRKCSH mutations leads to autosomal dominant polycystic liver disease. Hepatology 39:924–931

Elsayes KM, Narra VR, Yin Y, Mukundan G, Lammle M, Brown JJ (2005) Focal hepatic lesions: diagnostic value of enhancement pattern approach with contrast-enhanced 3D gradient-echo MR imaging. Radiographics 25:1299–1320

Esseghaier S, Aidi Z, Toujani S, Daghfous MH (2017) A starry sky: multiple biliary hamartomas. Presse Med 46:787–788

Gabow PA (1993) Autosomal dominant polycystic kidney disease. N Engl J Med 329:332–342

Gaines PA, Sampson MA (1989) The prevalence and characterization of simple hepatic cysts by ultrasound examination. Br J Radiol 62:335–337

Gevers TJ, Hol JC, Monshouwer R, Dekker HM, Wetzels JF, Drenth JP (2015) Effect of lanreotide on polycystic liver and kidneys in autosomal dominant polycystic kidney disease: an observational trial. Liver Int 35:1607–1614

Giambelluca D, Caruana G, Cannella R, Lo Re G, Midiri M (2018) The starry sky liver: multiple biliary hamartomas on MR cholangiopancreatography. Abdom Radiol 43:2529–2530

Guay-Woodford LM, Desmond RA (2003) Autosomal recessive polycystic kidney disease: the clinical experience in North America. Pediatrics 111: 1072–1080

Gunay-Aygun M, Gahl WA, Heller T (2008) Congenital hepatic fibrosis overview [Updated 2014 Apr 24]. In: Adam MP, Ardinger HH, Pagon RA et al (eds) GeneReviews® [Internet]. University of Washington, Seattle (WA). 1993–2019

Hogan MC, Masyuk TV, Page LJ, Kubly VJ, Bergstralh EJ, Li X, Kim B, King BF, Glockner J, Holmes DR 3rd, Rossetti S, Harris PC, LaRusso NF, Torres VE (2010) Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. J Am Soc Nephrol 21:1052–1061

Horton KM, Bluemke DA, Hruban RH, Soyer P, Fishman EK (1999) CT and MR imaging of benign hepatic and biliary tumors. Radiographics 19:431–451

Jain D, Sarode VR, Abdul-Karim FW, Homer R, Robert ME (2000) Evidence for the neoplastic transformation of von Meyenburg complexes. Am J Surg Pathol 24:1131–1139

Jordon D, Harpaz N, Thung SN (1989) Caroli's disease and adult polycystic kidney disease: a rarely recognized association. Liver 9:30–35

Jung G, Benz-Bohm G, Kugel H, Keller KM, Querfeld U (1999) MR cholangiography in children with autosomal recessive polycystic kidney disease. Pediatr Radiol 29:463–466

Kassahun WT, Kahn T, Wittekind C, Mössner J, Caca K, Hauss J, Lamesch P (2005) Caroli's disease: liver resection and liver transplantation. Experience in 33 patients. Surgery 138:888–898

Kerr DN, Harrisson CV, Sherlock S, Walker RM (1961) Congenital hepatic fibrosis. Q J Med 30:91–117

Lazaridis KN, Strazzabosco M, Larusso NF (2004) The cholangiopathies: disorders of biliary epithelia. Gastroenterology 127:1565–1577

Lendoire J, Barros Schelotto P, Alvarez Rodríguez J, Duek F, Quarin C, Garay V, Amante M, Cassini E, Imventarza O (2007) Bile duct cyst type V (Caroli's disease): surgical strategy and results. HPB 9:281–284

Lendoire JC, Raffin G, Grondona J, Bracco R, Russi R, Ardiles V, Gondolesi G, Defelitto J, de Santibañes E, Imventarza O (2011) Caroli's disease: report of surgical options and long-term outcome of patients treated in Argentina. Multicenter study. J Gastrointest Surg 15:1814–1819

Lewis S, Vasudevan P, Chatterji M, Besa C, Jajamovich G, Facciuto M, Taouli B (2016) Comparison of gadoxetic acid to gadobenate dimeglumine for assessment of biliary anatomy of potential liver donors. Abdom Radiol 41:1300–1309

Lonergan GJ, Rice RR, Suarez ES (2000) Autosomal recessive polycystic kidney disease: radiologic-pathologic correlation. Radiographics 20:837–855

Mamone G, Carollo V, Cortis K, Aquilina S, Liotta R, Miraglia R (2019) Magnetic resonance imaging of fibropolycystic liver disease: the spectrum of ductal plate malformations. Abdom Radiol 44:2156–2171

Mehta L, Jim B (2017) Hereditary renal diseases. Semin Nephrol 37:354–361

Meijer E, Visser FW, van Aerts RMM, Blijdorp CJ, Casteleijn NF, D'Agnolo HMA, Dekker SEI, Drenth JPH, de Fijter JW, van Gastel MDA, Gevers TJ, Lantinga MA, Losekoot M, Messchendorp AL, Neijenhuis MK, Pena MJ, Peters DJM, Salih M, Soonawala D, Spithoven EM, Wetzels JF, Zietse R, Gansevoort RT, DIPAK-1 Investigators (2018) Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease: the DIPAK 1 randomized clinical trial. JAMA 320:2010–2019

Morgan DE, Lockhart ME, Canon CL, Holcombe MP, Bynon JS (2006) Polycystic liver disease: multimodality imaging for complications and transplant evaluation. Radiographics 26:1655–1668

Neijenhuis MK, Wijnands TFM, Kievit W, Ronot M, Gevers TJG, Drenth JPH (2019) Symptom relief and not cyst reduction determines treatment success in aspiration sclerotherapy of hepatic cysts. Eur Radiol 29:3062–3068

O'Brien K, Font-Montgomery E, Lukose L, Bryant J, Piwnica-Worms K, Edwards H, Riney L, Garcia A, Daryanani K, Choyke P, Mohan P, Heller T, Gahl WA, Gunay-Aygun M (2012) Congenital hepatic fibrosis and portal hypertension in autosomal dominant polycystic kidney disease. J Pediatr Gastroenterol Nutr 54:83–89

Paul BM, VandenHeuvel GB (2014) Kidney: polycystic kidney disease. Wiley Interdiscip Rev Dev Biol 3:465–487

Perugorria MJ, Masyuk TV, Marin JJ, Marzioni M, Bujanda L, LaRusso NF, Banales JM (2014) Polycystic liver diseases: advanced insights into the molecular mechanisms. Nat Rev Gastroenterol Hepatol 11:750–761

Principe A, Lugaresi ML, Lords RC, D'Errico A, Polito E, Gallö MC, Bicchierri I, Cavallari A (1997) Bile duct hamartomas: diagnostic problems and treatment. Hepatogastroenterology 44:994–997

Ramond MJ, Huguet C, Danan G, Rueff B, Benhamou JP (1984) Partial hepatectomy in the treatment of Caroli's disease. Report of a case and review of the literature. Dig Dis Sci 29:367–370

Redston MS, Wanless IR (1996) The hepatic von Meyenburg complex: prevalence and association with hepatic and renal cysts among 2843 autopsies. Mod Pathol 9:233–237

Rogers TN, Woodley H, Ramsden W, Wyatt JI, Stringer MD (2007) Solitary liver cysts in children: not always so simple. J Pediatr Surg 42:333–339

Russell RT, Pinson CW (2007) Surgical management of polycystic liver disease. World J Gastroenterol 13:5052–5059

Santiago I, Loureiro R, Curvo-Semedo L, Marques C, Tardáguila F, Matos C, Caseiro-Alves F (2012) Congenital cystic lesions of the biliary tree. Am J Roentgenol 198:825–835

Sayma M, Walters HR, Hesford C, Tariq Z, Nakhosteen A (2019) Rapidly enlarging, giant hepatic cyst growing pseudomonas. BMJ Case Rep 1:12

Semelka RC, Hussain SM, Marcos HB, Woosley JT (1999) Biliary hamartomas: solitary and multiple lesions shown on current MR techniques including gadolinium enhancement. J Magn Reson Imaging 10:196–201

Shneider BL, Magid MS (2005) Liver disease in autosomal recessive polycystic kidney disease. Pediatr Transplant 9:634–639

Song JS, Lee YJ, Kim KW, Huh J, Jang SJ, Yu E (2008) Cholangiocarcinoma arising in von Meyenburg complexes: report of four cases. Pathol Int 58:503–512

Srinath A, Shneider BL (2012) Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. J Pediatr Gastroenterol Nutr 54:580–587

Summerfield JA, Nagafuchi Y, Sherlock S, Cadafalch J, Scheuer PJ (1986) Hepatobiliary fibropolycystic diseases. A clinical and histological review of 51 patients. J Hepatol 2:141–156

Torres VE, Harris PC, Pirson Y (2007) Autosomal dominant polycystic kidney disease. Lancet 369: 1287–1301

Turkbey B, Ocak I, Daryanani K, Font-Montgomery E, Lukose L, Bryant J, Tuchman M, Mohan P, Heller T, Gahl WA, Choyke PL, Gunay-Aygun M (2009) Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis (ARPKD/CHF). Pediatr Radiol 39:100–111

van de Laarschot LFM, Drenth JPH (2018) Genetics and mechanisms of hepatic cystogenesis. Biochim Biophys Acta Mol Basis Dis 1864:1491–1497

van Keimpema L, de Koning DB, Strijk SP, Drenth JP (2008) Aspiration-sclerotherapy results in effective control of liver volume in patients with liver cysts. Dig Dis Sci 53:2251–2257

van Keimpema L, Nevens F, Vanslembrouck R, van Oijen MG, Hoffmann AL, Dekker HM, de Man RA, Drenth JP (2009) Lanreotide reduces the volume of polycystic

liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology 137:1661–1668. e1–2

Veigel MC, Prescott-Focht J, Rodriguez MG, Zinati R, Shao L, Moore CA, Lowe LH (2009) Fibropolycystic liver disease in children. Pediatr Radiol 39:317–327

Venkatanarasimha N, Thomas R, Armstrong EM, Shirley JF, Fox BM, Jackson SA (2011) Imaging features of ductal plate malformations in adults. Clin Radiol 66:1086–1093

von Meyenburg H (1918) Uber die cystenliber. Beitr Pathol Anat 64:477e532

Willey CJ, Blais JD, Hall AK, Krasa HB, Makin AJ, Czerwiec FS (2017) Prevalence of autosomal dominant polycystic kidney disease in the European Union. Nephrol Dial Transplant 32:1356–1363

Xu AM, Xian ZH, Zhang SH, Chen XF (2009) Intrahepatic cholangiocarcinoma arising in multiple bile duct hamartomas: report of two cases and review of the literature. Eur J Gastroenterol Hepatol 21: 580–584

Yang XY, Zhang HB, Wu B, Li AJ, Fu XH (2017) Surgery is the preferred treatment for bile duct hamartomas. Mol Clin Oncol 7:649–653

Yoshida H, Onda M, Tajiri T, Mamada Y, Taniai N, Mineta S, Hirakata A, Futami R, Arima Y, Inoue M, Hatta S, Kishimoto A (2003) Infected hepatic cyst. Hepato-Gastroenterology 50:507–509

Zeitoun D, Brancatelli G, Colombat M, Federle MP, Valla D, Wu T, Degott C, Vilgrain V (2004) Congenital hepatic fibrosis: CT findings in 18 adults. Radiology 231:109–116

Zerres K, Mücher G, Becker J, Steinkamm C, Rudnik-Schöneborn S, Heikkilä P, Rapola J, Salonen R, Germino GG, Onuchic L, Somlo S, Avner ED, Harman LA, Stockwin JM, Guay-Woodford LM (1998) Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): molecular genetics, clinical experience, and fetal morphology. Am J Med Genet 76:137–144

Zheng RQ, Zhang B, Kudo M, Onda H, Inoue T (2005) Imaging findings of biliary hamartomas. World J Gastroenterol 11:6354–6359