Congenital and Development Disorders of the Liver

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Contents

Abstract

In this chapter we present the congenital anomalies of the hepatic vasculature system and biliary tract. The alterations are determined during the complex development that occurs between the fourth and the tenth weeks of embryonic life together with the ductal plate malformation; they constitute the basis for the study and understanding of the following paragraphs.

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1 Congenital Portosystemic Venous Shunt: Abernethy Malformation

1.1 Clinical Features

Congenital absence of the portal vein is an important finding as the complete loss of portal perfusion predisposes the liver to focal or diffuse hyperplastic or dysplastic changes, involving neurological, pulmonary, metabolic, and other systems. In 1793 John Abernethy, a surgeon, for the first time, described an autopsy of a 10-month-old female and showed termination of the portal vein (PV) in the inferior vena cava at

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the level of the renal veins (complete portosystemic shunt) (Abernethy 1793). An aberrant development of the portal vein or vena cava in early embryonic life explains the genesis of congenital portosystemic shunts (CPSS) (Ghuman et al. 2016). Congenital portosystemic venous shunt (PSVS) has been explained by alterations in the embryological development of the portal system and inferior vena cava (IVC) with abnormal involution of the vitelline veins that occur between the fourth and tenth weeks of embryonic life (Bhargava et al. 2011) and maybe depends on the anatomical site (right or left) and level (proximal or distal) at which the vitelline veins fail to differentiate. Instead a patent ductus venosus (Kamimatsuse et al. 2010) acts as an intrahepatic shunt and may result in hypoplasia of the portal vein due to an alteration in hemodynamics from congenital heart defects. For further details see the section on embryology of the liver (chapter "Embryology and Development of the Liver").

Portosystemic shunts can be congenital or acquired due to portal hypertension. PSVS is a rare condition and is classified into two major categories, intrahepatic and extrahepatic variants according to the site of the shunt. Congenital extrahepatic portosystemic venous shunt (EPSVS) is a rare condition in which the porto-mesenteric blood drains into a systemic vein, bypassing the liver through a complete or partial shunt; in this condition the anastomoses are established between a systemic vein and the porto-mesenteric vasculature before division of the portal vein (PV). Morgan and Superina (1994) classified EPSVS into two types; in type 1 there is a complete diversion of portal blood into the systemic circulation (*end-to-side shunt*), with absent intrahepatic portal branches (Fig. 1). Moreover type 1 shunt is subdivided into two classes in which splenic vein (SV) and superior mesenteric vein (SMV) drain separately into a systemic vein—inferior vena cava (type 1a)—those in which drain together after joining to form a common trunk (type 1b) (Howard and Davenport 1997). In type 1 EPSVS liver is not perfused with portal blood because of complete shunt of portal blood flow into systemic circulation and liver transplantation is the only effective

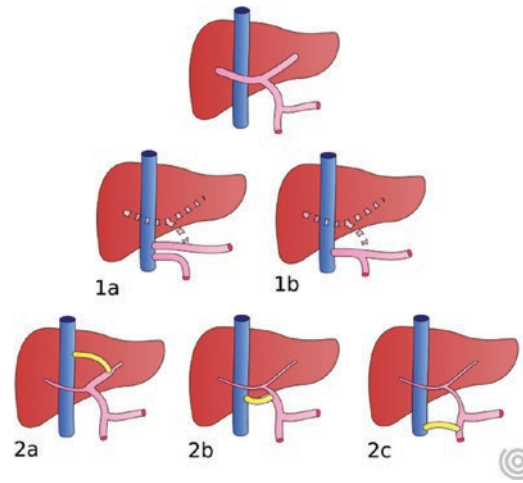

Fig. 1 Classification of congenital extrahepatic portosystemic shunts (blue line: inferior vena cava (IVC); red line: splenic vein (SV) and superior mesenteric vein (SMV) and portal vein branches; yellow line: shunt). Normal anatomy of hepatic vasculature in the first figure above. Shunts before main portal vein division with "congenital absence of portal vein." Type 1: end-to-side shunt; type 1a: splenic vein (SV) and superior mesenteric vein (SMV) drain separately into inferior vena cava (IVC); type 1b: the SV and SMV drain together after joining to form a common trunk without supplying the liver. Type 2: the portal vein (PV) is normal or hypoplastic. Type 2a shunts arise from portal vein branches and include the patent ductus venous. In type 2b the shunts arise from the main portal vein, its bifurcation, or porto-mesenteric confluence. Type 2c porto-hepatic shunt is peripheral and arises from gastric, mesenteric, or splenic veins

treatment in critical cases. In type 2 EPSVS (Lautz et al. 2011) the intrahepatic portal vein (PV) is intact, but some of the portal flow is switched into a systemic vein through a *side-to-side shunt* (Fig. 1). Patients with type 1a EPSVS shunt are usually girls with cardiac or other congenital anomalies, including biliary atresia, oculo-auriculo-vertebral dysplasia (Goldenhar syndrome), situs inversus and polysplenia (Marois et al. 1979), and hepatic masses (Motoori et al. 1997). Type 1b EPSVS shunt usually occurs in boys without other associated anomalies or hepatic masses (Kohda et al. 1999). Patients with type 2 EPSVS shunts do not present gender preference and have fewer associated malformations (Murray et al. 2003).

Type 2 exhibits partial shunting and a hypoplastic portal vein with preserved hepatic flow and is subdivided into three forms: shunt type 2a

arising from left or right portal vein (includes patent ductus venosus) (Uchino et al. 1999); shunt type 2b arising from a position between the bifurcation of the portal vein and the splenomesenteric confluence (Mboyo et al. 1995); and shunt type 2c arising from the mesenteric (or its superior rectal tributaries), gastric, or splenic veins and flowing into the renal vein, azygos vein, iliac veins, or their branches (Mizoguchi et al. 2001). In this case persistent portal circulation allows shunt surgical closure or embolization (Hu et al. 2008; Stringer 2008).

Intrahepatic portosystemic venous shunt (IPSVS) is an abnormal intrahepatic communication >1 mm in diameter between the intrahepatic portal vein and the hepatic veins or IVC. Park et al. (1990) subdivided them into type 1 (a single large vessel runs from the right branch of portal vein to the posterior surface of the livers and enters inferior vena cava); type 2 (a localized peripheral shunt in one hepatic segment that has one or more communications between peripheral branches of portal and hepatic veins); type 3 (an aneurysmal communication between peripheral portal vein and hepatic veins); type 4 (multiple communications between peripheral portal and hepatic veins are present in both lobes); and type 5 (persistent ductus venosus). The first two types are the most common. Embolization or surgery is performed if the shunt is symptomatic.

Congenital portosystemic venous shunts (PSVS) are rare (1/30,000 births) (Bernard et al. 2012) and their clinical manifestations are various and can be divided into three types:

- *Conditions due to the abnormal liver development*: adenoma, focal nodular hyperplasia (Grazioli et al. 2000), hemangioma due to the alteration in local hemodynamics, hepatic ischemia with the compensatory increase in arterial flow, and associated elevated circulating levels of hepatic growth factors (e.g., insulin, glucagon, hepatocyte growth factor). Possible evolution into hepatoblastoma and hepatocellular carcinoma has been reported (Pupulim et al. 2013).
- *Shunt-related symptoms* such as hepatic encephalopathy for the increase of serum levels of ammonia, galactose, and other toxic metabolites that cannot be absorbed by the failing liver (Murray et al. 2003); hepato-pulmonary syndrome and pulmonary hypertension due to the deviation of vasoactive mediators in the systemic circulation, with consequent dilation of intrapulmonary vessels, are the most prominent manifestations caused by long-term portosystemic shunting (Sokollik et al. 2013).
- *Symptoms secondary to the congenital anomalies associated* (Badea et al. 2012) with abnormalities such as polysplenia (Newman et al. 2010), congenital heart disease (septal defects, patent ductus arteriosus, tetralogy of Fallot), biliary system (congenital biliary atresia, choledochal cyst), malrotation, duodenal atresia, annular pancreas, situs inversus, anomalies of the renal tract (cystic dysplasia of kidneys), skeletal anomalies (radial hypoplasia), Down syndrome (Figs. 2 and 3), and Turner syndrome (Kim et al. 2012) (Table 1).

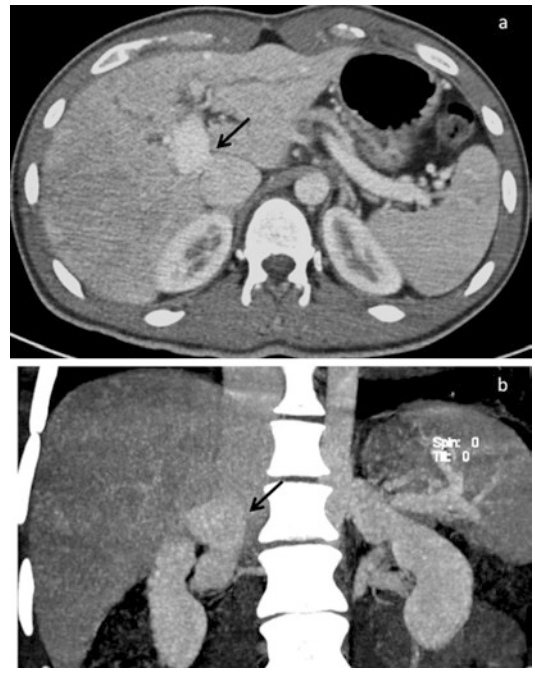

Fig. 2 Type 2. Contrast-enhanced CT, transverse (**a**) and coronal (**b**) planes. Portal vein is patent. Shunt (black arrow) between the intrahepatic portal vein and the inferior vena cava (**a**) placed cranially to the right renal vein (**b**) and caudally to the hepatic veins

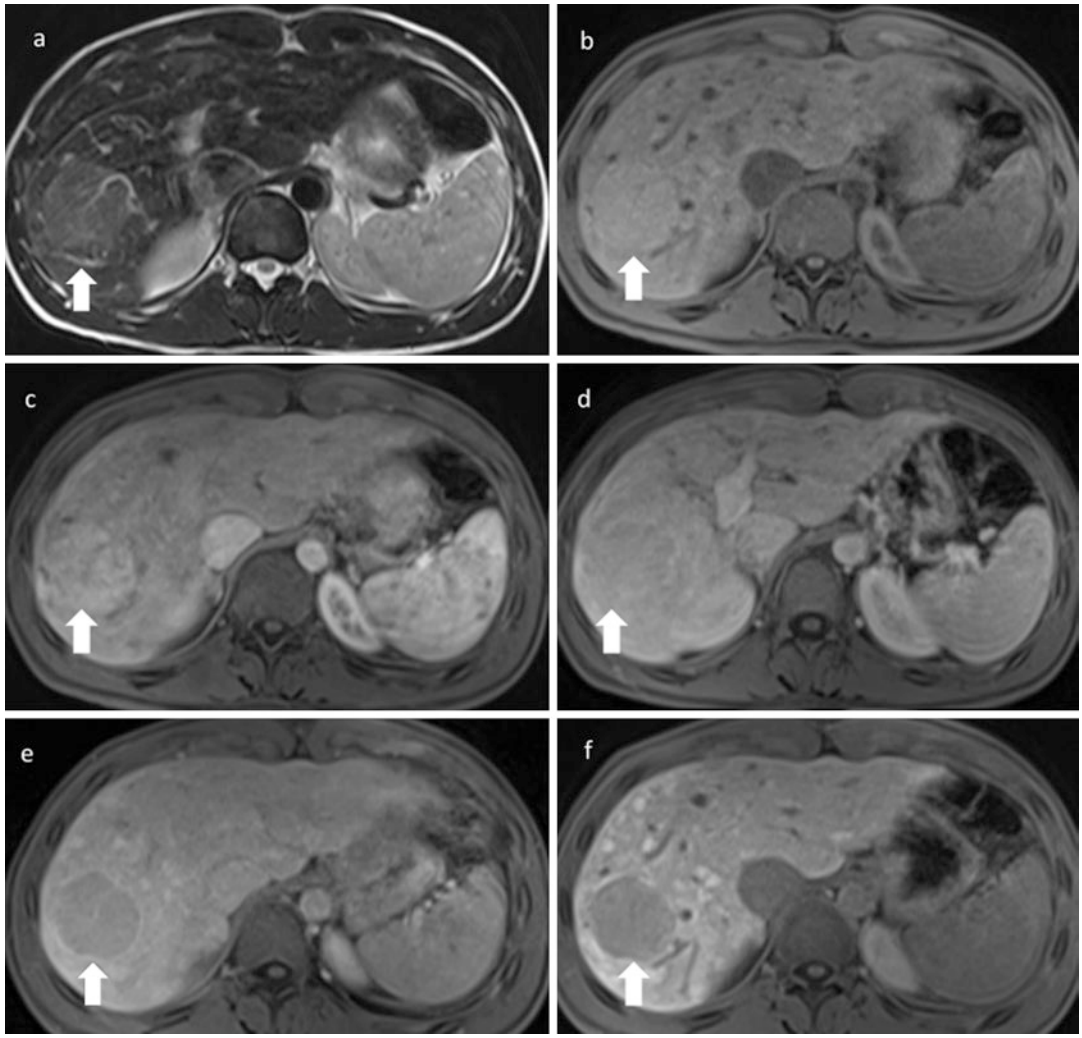

Fig. 3 Hepatic adenoma proven histologically in a 26-year-old boy with Down syndrome and Abernethy syndrome. On MR mass of 4 cm in the right hepatic lobe tenuously hyperintense on T2-w (**a**) and iso-hyperintense on T1-w fat sat pre-contrast (**b**) and post-contrast enhancement: tenuously hyperintense on arterial phase (**c**), isointense on portal phase (**d**), hypointense on late phase (**e**) and hepatobiliary phase (**f**)

Table 1 Congenital anomalies associated with congenital portosystemic shunt

Cardiovascular	*Gastrointestinal*
Atrial ventricular septal defect	Polysplenia
Patent ductus arteriosus	Biliary atresia
Ventricular septal defect	Choledochal cyst
Tetralogy of Fallot	Annular pancreas
Dextrocardia*	Duodenal atresia
Mesocardia*	*Genitourinary anomalies*
Congenital stenosis of aortic valve*	Multicystic dysplastic kidney
Vascular anomalies	Bilateral ureteropelvic stenosis
Double inferior vena cava	Vesicoureteral reflux
Interruption of the inferior vena cava	Crossed fused renal ectopia
Genetic syndromes	Hypospadias
Down, Bannayan-Riley-Ruvalcaba, Turner, Holt-Oram,	*Cutaneous vascular malformations and tumors*
Grazioli and Goldenhar, LEOPARD, Rendu-Osler-Weber,	*Skeletal anomalies*
Noonan	*Rarely observed

1.2 Imaging Findings

Most often, the diagnosis is made primarily with US and Doppler US when patients undergo an US scan for other reasons. CT angiography (Prokop 2000) and MR angiography (MRA) are used for further classification of the shunt and assessment of accompanying anomalies. DSA is necessary when results of the other tests disagree or are inconclusive for hepatic and portal vein pressure measurement or when TIPS positioning and portal vein embolization are necessary. About imaging CT or MR (Gallego et al. 2004) combined with Doppler US permits a comprehensive evaluation of morphologic and functional abnormalities of the portal system.

According to the diagnostic criteria proposed by Ohwada et al. (1994), it is possible to diagnose congenital portosystemic shunts in the absence of hypersplenism and portal hypertension; in the absence of remarkable microscopic change in liver samples, and not like those that occur in the course of idiopathic portal hypertension, hepatitis, or cirrhosis, the portal vein must be hypoplastic without arterio-portal fistula; there are no previous stories of abdominal surgery or inflammation.

US is the first-choice test because it is noninvasive and does not expose to ionizing radiation and it is neither necessary to seduce young patients. The experience and a good operator, associated with a careful knowledge of the anatomy of the hepatic and abdominal vessels and related venous abnormalities, contribute to accurate diagnosis of EPSVS (Hu et al. 2008). A decrease in the size of the liver or an increase in echogenicity of the periportal spaces can be observed; however these findings are nonspecific. The US findings include abnormal cystic or tubular, anechoic, serpiginous vascular structures which seem to communicate the portal with the systemic circulation (Tsitouridis et al. 2009). Moreover, this method is also widely used for prenatal screening or as an intraoperative investigation technique (Achiron et al. 2009). US may fail to accurately demonstrate the associated extrahepatic shunts (Massin et al. 1999; Nakasaki et al. 1989). Therefore, once the anomaly has been identified, it is passed to Doppler US which is useful for determining the flow direction of the identified vessels (Konno et al. 1997). Doppler US study can confirm the vascular nature of the structures and calculate the shunt ratio (total blood flow volume in the shunt divided by the blood flow in the portal vein). It has been recommended that a shunt ratio greater than 60% should be corrected to prevent complications (Ohwada et al. 1994).

These patients usually do not present portal hypertension imaging characteristics such as ascites, varices, or splenomegaly (Murray et al. 2003). CT and MRI are useful to confirm the diagnosis of congenital portosystemic shunt and to identify the absent vessels and the type of vascular malformation (Gallego et al. 2004; Kornprat et al. 2005). Post-processing techniques, such as maximum intensity projection, multiplanar reformation, and volume rendering, provide additional information. MRA can also confirm congenital absence of portal vein and visualize the portosystemic shunt (Kornprat et al. 2005). Multidetector CT has also been shown to show small vascular branches and has a spatial resolution higher than the MRI (Prokop 2000). However, the use of CT in evaluating these patients is not regularly recommended because it involves exposure to ionizing radiation, as these are very often paediatric patients. MRI is also a reliable and noninvasive diagnostic modality for the portal venous system (Usuki and Miyamoto 1998). MR imaging can be used in the diagnosis of congenital portosystemic shunt but the definitive diagnosis can only be made with catheter DSA (Matsuoka et al. 1992) and with additional histological analysis of the hepatic parenchyma that demonstrates the absence of hepatic portal venules within the portal triad (Collard et al. 2006). However, DSA has the disadvantage of exposure to radiation and requires anesthesia and a vascular puncture with its complications. DSA is not the gold standard for children, even if it is safe enough (Usuki and Miyamoto 1998). For these reasons DSA is reserved only in cases in which treatment is considered necessary. Indirect mesenteric porto-venography is usually the angiographic technique used to clarify the anatomy of the portal system and depict the characteristics of an extrahepatic shunt. This tech-

nique is performed during the visceral phase of mesenteric arteriography. When it cannot provide a distinct image of the shunt, transhepatic percutaneous portography may be required. With this technique, selective embolization can be performed in type 2 shunt as a possible therapy. Transvenous liver biopsy and measurement of pressure gradients can also be performed at the same time (Hu et al. 2008). Finally the portal scintigraphy performed with rectal administration of iodine 123-iodoamphetamine may be for the evaluation of type 2 shunts and for calculating the shunt ratio. The portosystemic shunt index is calculated dividing the lung accounts for the liver and lung counts (Kashiwagi et al. 1988). Shunt reports of more than 5% are considered abnormal (Uchino et al. 1996). If a portosystemic shunt is present, the isotope is detected in liver and lungs simultaneously.

Imaging is useful also for the evaluation of focal hepatic lesions (regenerative nodular hyperplasia, focal nodular hyperplasia, or hepatocellular adenoma) (Goo 2007) that very often occur in patients with this malformation and that present a histological variety in the nature of the nodules but their growth and development seem to depend on the degree of arterial supply. In particular regenerative nodular hyperplasia and focal nodular hyperplasia are more often atypical than in patients with normal livers and may enlarge over time; for complete and chronic portal deprivation often there are atypias (Kim et al. 2004).

Nodular regenerative lesions on MRI are homogeneous, well defined, and frequently multiple; on T1-w images are hyperintense, on T2-w images are more variable, and on T2-w images are isointense to slightly hyperintense. The lesions show arterial hyperenhancement and remain isointense to slightly hyperintense on portal venous, equilibrium, and delayed-phase images. This tendency for these lesions to remain hyperintense on portal venous and delayed phases is different from other benign lesions that become isointense as well as from HCC that shows venous phase washout and appears hypointense to the liver parenchyma (Alonso-Gamarra et al. 2011). The contrastographic behavior is the same also on CT and CEUS (Bartolozzi and Lencioni 2001). Another aspect that distinguishes them is the absence of fat (present instead in the adenoma), calcification, and hemorrhage. Some may be surrounded by a peripheral hypointense border on MRI, hypodense border on the CT images, and a hypoechoic border on US, due to sinusoidal dilation and marked congestion in the surrounding liver (the "sign of the halo") (Wanless 1990). A "coral atoll-like appearance" has also been reported on US for nodular regenerative hyperplasia. This refers to a peripheral hyperechoic rim surrounding a focal liver lesion (Caturelli et al. 2011).

MRI of the brain (Córdoba 2011) may reveal deposition of paramagnetic substances in the basal ganglia related to chronic portosystemic shunting and white matter atrophy or a hyperintense basal ganglia (globus pallidus) on T1-w images.

For this rare condition it is important to focalize the presence or absence of hepatic portal vein supply and the course of the shunt to decide the appropriate therapeutic option; imaging plays a crucial role in the diagnosis and follow-up of patients.

2 Simple Cysts

The detection of hepatic cysts in subjects who undergo an imaging examination for other reasons is not infrequent. The finding of hepatic cysts is more common in women (Farges and Aussilhou 2012). Based on margins and content, hepatic cysts can be divided into simple and complex cysts. This distinction is important because it may be necessary to make further diagnoses and treatments. Simple hepatic cysts are generally round or ovoid structures that have a subtle wall. Microscopically, the liver cysts contain serous liquid, bile-like fluid, and are covered with a single layer of cuboidal epithelial cells, and a thin rim of fibrous stroma around. Their origin derives from aberrant bile ducts that have lost communication with the biliary tree and continue to secrete intraluminal fluid (Benhamou and

Menu 1994). Probably they originate from hamartomatous tissue (Van Sonnenberg et al. 1994). Hepatic cysts are common and are presumed to be present in almost 2.5% of the population. They are almost always asymptomatic. They can also reach considerable sizes of up to 30 cm (Mathieu et al. 1997). Complex cysts (Table 2) have internal septa, wall thickening, or nodularity, which may present contrast enhancement to radiological investigations; the fluid contains debris, or proteinaceous or hemorrhagic material. Complex cysts may be of neoplastic, inflammatory, infectious, or post-traumatic origin or even present other etiologies (Vachha et al. 2011). Intracystic hemorrhage is a rare complication of simple cysts and usually presents with severe abdominal pain (Salemis et al. 2007), although in some cases it may be completely asymptomatic (Kitajima et al. 2003). Hepatic cysts are generally asymptomatic and treatment with aspiration sclerotherapy or with laparoscopic or open surgical fenestration techniques (Moorthy et al. 2001) of the cyst may be necessary when they reach large dimensions to avoid complications such as biliary obstruction, rupture with hemorrhage, and hemoperitoneum.

Table 2 US findings of hepatic cyst

Simple cyst	Complex cyst
Thin, smooth walls	Mural irregularity or nodularity
Zero to two septa	Septated
Anechoic content	Debris, calcification, fluid levels

The feedback of the following characteristics allows an highly likely diagnosis of cyst: spherical or oval in shape, with smooth and sharp edges and strong echoes of the rear walls (which indicate an interface fluid/well-defined tissue) in an anechoic content (i.e., cavity filled with liquid), without septa (Spiegel et al. 1978). After CEUS, simple cysts (or those complicated by hemorrhage or infection) show no vascularization of contents and walls in all the vascular phases (Vidili et al. 2018). On CT a simple hepatic cyst appears round or ovoid, well defined, homogeneous, with hypo-attenuation (0–10 UH) which does not improve after intravenous contrast medium administration. The uncomplicated cysts are almost never septate (Murphy et al. 1989). MRI also shows a well-defined lesion content liquid that does not show contrast enhancement. On the basis of these features, imaging alone is sufficient to establish an accurate diagnosis (Figs. 4 and 5) and follow-up of a simple hepatic cyst (Mathieu et al. 1997).

3 Ductal Plate Malformation

Ductal plate malformations represent a complex continuum of pathological abnormalities encountered depending on the level of the biliary tree affected (intrahepatic and/or extrahepatic biliary ducts; large, medium, or smaller intrahepatic biliary ducts) during embryogenesis. Jorgensen

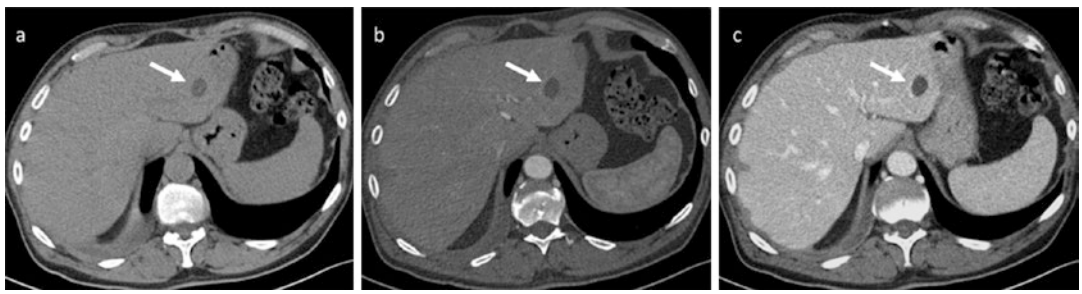

Fig. 4 Simple hepatic cyst (arrow) on (**a**) unenhanced and contrast-enhanced CT on (**b**) hepatic arterial and (**c**) portal venous phase

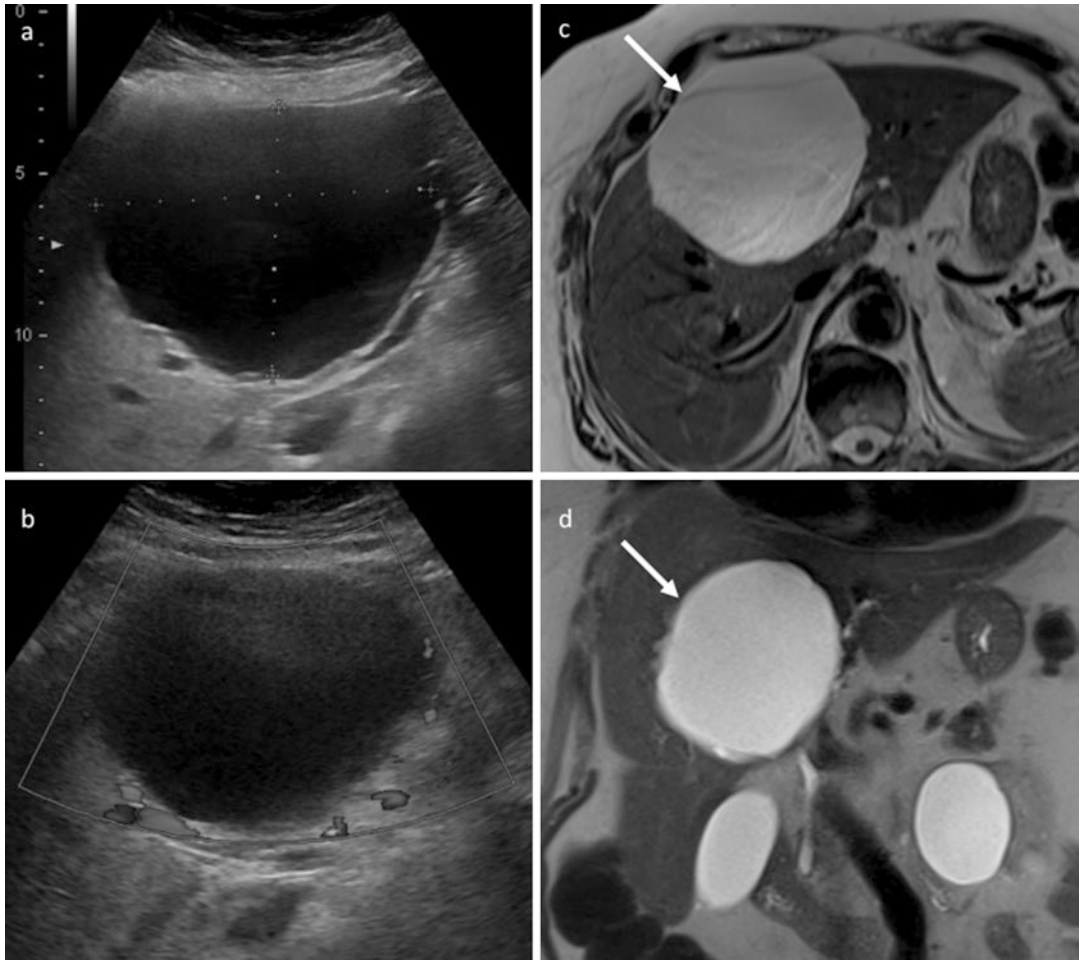

Fig. 5 Large hepatic cyst (calipers) with diffuse posterior acoustic enhancement on grayscale US (**a**) and on color Doppler US (**b**); T2-w turbo spin-echo MRI sequence on transverse (**c**) and coronal planes (**d**). The cystic lesion (arrow) appears hyperintense without evidence of peripheral capsule or septa

(1977) was the first to describe ductal plate malformations in 1977. The ductal plate is a transient structure along the branches of the portal vein, in the embryonic life, and corresponding to the most immature state of the bile duct. During the first 8 weeks after fertilization, the developing liver is composed only of hepatoblasts, along portal vein; no bile ducts have yet formed (Desmet 1992). These hepatoblasts are bipotential cells and are capable of differentiating into hepatocytes or cholangiocytes (bile duct cells) (Desmet 1992; Krause et al. 2002). The hepatoblast cell layer in contact with mesenchyme surrounding the portal vein produces cytokeratins 8 and 18 present in the hepatoblasts, to which is added the cytokeratin 7 marker of the biliary cells. This layer of cells joins with a second layer to create a double-epithelial cylinder of biliary cell type, called the ductal plate (Lonergan et al. 2000). A narrow lumen is present between these ductal plate layers. During the next several weeks, ductal plate remodeling occurs in three

phases. First, several focal dilatations, called peripheral tubules, form between the two ductal plate layers and become the intrahepatic bile ducts (Hassan and Ellethy 2014). Second, with continued remodeling of the ductal plate, the hepatic artery branch appears in the periportal mesenchyme. Finally, the peripheral tubules become incorporated into the periportal mesenchyme, and residual non-tubular segments of the ductal plate disappear by apoptosis. Thus, within each portal triad, a tubular bile duct is surrounded by portal connective tissue. Any interruption in the remodeling of the ductal plate may result in persistence of the excess embryonic epithelial duct structures, called exactly ductal plate malformation (Jorgensen 1977) which can affect the intra- or extrahepatic biliary ductal system further delineating the spectrum of clinic-pathological appearances; for example, malformations of the larger extrahepatic biliary ducts result in choledochal cysts; involvement of large- and medium-sized intrahepatic ducts results in Caroli disease and autosomal dominant polycystic liver disease—ADPLD—(for the latter see chapter "Fibropohlycystic Liver Diseases"), respectively; small-sized intrahepatic duct involvement results in biliary hamartomas and congenital hepatic fibrosis (Fig. 6).

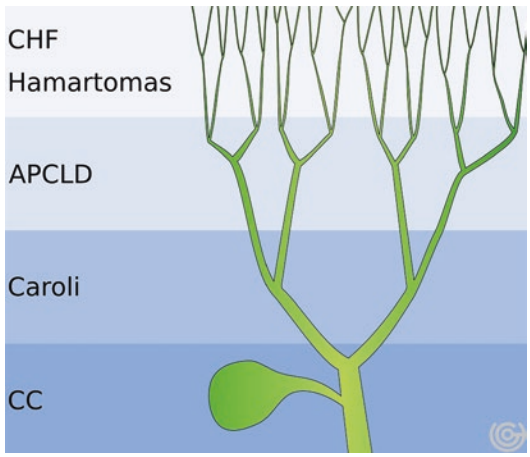

Fig. 6 Schematic illustration showing the types of ductal plate malformations depending on the duct size affected. *CHF* congenital hepatic fibrosis, *APLD* adult polycystic liver disease, *CC* choledochal cysts

3.1 Biliary Hamartomas

Biliary hamartomas (BH), also known as microhamartomas or von Meyenburg complex, because initially described by the Swiss pathologist Hanns von Meyenburg in 1918, are considered as malformation of small intralobular bile ducts (Yonem et al. 2006) embedded in abundant fibrous stroma; they are benign hepatic lesions resulting from developmental malformation of the ductal plate (Desmet 2005). According to Raynaud et al. (2011) there are three main mechanisms that can explain the malformations of the ductal plate, in particular when the apicobasal polarity is systematically interrupted. These mechanisms consist of abnormal differentiation of hepatoblasts in bile cells, abnormal maturation of the primitive biliary structure in bile ducts, and abnormal expansion of the duct. BH are a rare and usually isolated asymptomatic entity, and are usually discovered incidentally (Karahan et al. 2007). They are seen in 5.6% of adults and 0.9% of children at autopsy, and often are associated with polycystic kidney and liver disease (Redston and Wanless 1996). Patients with BH have relatively small cystic lesions, ranging in size from less than 5–10 mm in diameter (Luo et al. 1998), but some may reach up to 3 cm and BH are multiple, up to about 10, scattered throughout both liver lobes, predominantly in the subcapsular and periportal areas. Microscopically, they consist of irregularly shaped, dilated, branching bile ducts surrounded by abundant fibrous stroma. The ducts have a cuboidal epithelial lining and can contain bile or amorphous materials (Duran-Vega et al. 2000). Typically, BH appear well circumscribed but not encapsulated and might be exchanged with hepatic metastases, lymphoma, and simple liver cysts. In addition, BH are associated with increased risk of hepatobiliary carcinomas (Brancatelli et al. 2005). It is asymptomatic and does not compromise liver function. Definitive diagnosis requires liver biopsy (Zheng et al. 2005).

Imaging findings are usually not specific. On US BH present as innumerable tiny hypoechoic or hyperechoic lesion and are distributed uniformly throughout the liver that often appears

exactly heterogeneous and coarse (Pech et al. 2016). These tiny micronodules may demonstrate "comet-tail artifacts" (Lev-Toaff et al. 1995) which explains why they are difficult to differentiate from aerobilia and from intrahepatic stones. Bright echogenic foci without mass effect can be seen and are attributed to periductal fibrosis crowding the interface between dilated bile ducts (Tan et al. 1989). Differences in echogenicity may be due to the size of the dilated bile duct component, which, at a certain size, would behave like other microcystic structures and demonstrate echogenicity. The lesions that affect all segments of the liver give a "honeycomb" (Ryu et al. 2012) pattern with heterogeneous echo texture (Zheng et al. 2005). On CT the lesions are depicted as multiple, round, hypoattenuated lesions without enhancement after contrast medium administration and with dimension of less than 15 mm distributed throughout the liver (Brancatelli et al. 2005) in the subcapsular and periportal areas. They are difficult to characterize due to their small size and in some cases it is impossible to exclude the possibility that the lesions are small metastases, in particular in patients with known primary neoplasm. On precontrast T1- and T2-weighted MRI, lesions appear hypointense and hyperintense, respectively, and are generally well defined. On DWI MRI, they mimic cystic lesions. At MRCP (Fig. 7) the multiple tiny cystic lesions demonstrate no communication with the biliary tree. And also the nodules do not show enhancement after administration of hepatospecific contrast agents, because the lesions are independent and do not communicate with the biliary system (Mortele et al. 2002). The lesions may demonstrate thin rim enhancement with gadolinium, because the liver parenchyma that surrounds is compressed (Semelka et al. 1999). MRCP and, more generally, heavily T2-w MRI sequences are essential for differential diagnosis with Caroli disease (see below) (Krause et al. 2002). Differential diagnosis includes metastases, intrahepatic stones, peribiliary cysts, other ductal plate malformations such as Caroli disease and polycystic liver disease, and intrahepatic cholangiocarcinoma (Jain et al. 2010).

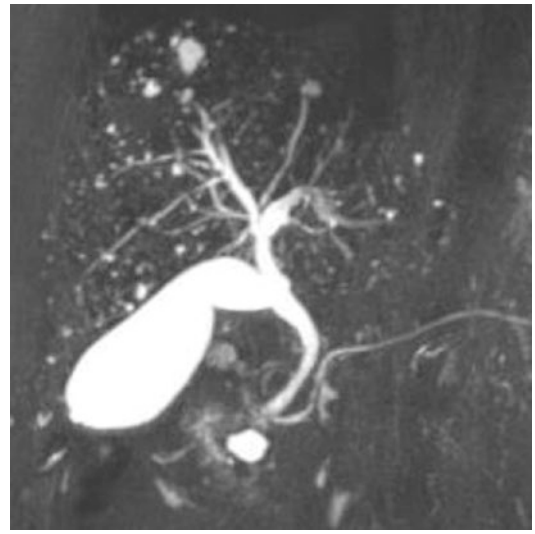

Fig. 7 Multiple biliary hamartomas in asymptomatic 55-year-old man. Three-dimensional T2-w MRCP with maximum intensity projection 3D reconstruction shows innumerable cysts that are nearly uniform in size and are distributed throughout the liver. The biliary tree has a normal appearance; MRI findings suggest biliary hamartomas

3.2 Congenital Hepatic Fibrosis (CHF)

CHF is a developmental malformation of ductal plate and is characterized by aberrant interlobular bile duct proliferation and periductal fibrosis. It is caused by a premature arrest in embryonic ductal plate into bile ducts. It can occur alone but almost always occurs in association with autosomal recessive polycystic kidney disease (Veigel et al. 2008). CHF associated with Caroli disease (dilatation of intrahepatic bile ducts) is denominated by Caroli syndrome (see above) (Ananthakrishnan and Saeian 2007); it may also be accompanied by other ductal plate malformations, including biliary cysts, von Meyenburg complex, and choledochal cyst or with associated renal abnormalities (renal tubular ectasia). It is a rare autosomal recessive disorder with a variable course affecting both the hepatobiliary and renal systems (Akhan et al. 2007). Associated renal conditions include renal dysplasia, autosomal recessive polycystic kidney disease (ARPKD) (Cobben et al. 1990), and nephronophthisis (medullary

cystic disease). CHF appears both sporadically and in a familial form. The age of onset ranges from early childhood to the fifth and sixth decades of life (Veigel et al. 2008). CHF has been described in four clinical forms: portal hypertensive, cholangitic, mixed portal hypertensive-cholangitic, and latent forms (D'agata et al. 1994). Symptoms may manifest early in life, in childhood, or in adult life, and include portal hypertension and upper gastrointestinal hemorrhage from ruptured esophageal varices (Kerr et al. 1978). Major complications of CHF consist of ascending cholangitis, hepatic failure, cirrhosis, and an increased risk of HCC. CHF consists histologically of broad, densely collagenous fibrous bands surrounding otherwise normal hepatic lobules. The fibrous band contains numerous small, uniform bile ducts, some of which can be dilated and irregularly shaped and can contain bile and traces of mucin. The ductal lining consists of cuboidal or low columnar epithelial cells. The hepatic parenchyma is subdivided by the overgrowth of portal fibrous tissue, while the regenerative activities of subdivided parenchyma are not evident, thus differing from cirrhotic regenerative nodules. In addition, portal vein branches are hypoplastic or unidentifiable in the fibrous portal tracts. Arterial branches are normal or hypoplastic, while the veins appear reduced in size. Inflammatory changes are not seen (Desmet 1998). In typical CHF, cysts are not visible due to their very small size. Liver biopsy is essential for diagnosis, but because of the firm consistency of the liver it may be difficult.

Imaging with US, CT, and MRI has roles in the evaluation of CHF. On US, CHF demonstrates increased or heterogeneous echogenicity, hyperechoic portal triads, and poorly defined portal vessels, secondary to fibrosis and ductular proliferation (Lowe and Schlesinger 2007). US can also evaluate biliary duct and liver parenchymal abnormalities, such as bile duct dilatation, regenerative nodules, hepatosplenomegaly, and periportal thickening (Akhan et al. 2007). Doppler US studies can be utilized to evaluate the patency of the portal vein and the flow direction in the portal and hepatic veins and detect portal hypertension in patients with suspected vascular complications related to liver cirrhosis. Zeitoun et al. (2004) retrospectively analyzed 18 patients with CHF. Suggestive morphological findings highly characteristic for CHF are hypertrophy of the left lateral segment and caudate, and normal or hypertrophic left medial segment and atrophic right lobe. Other hepatic elements related to CHF are varices, splenomegaly, portal hypertension, and periportal cuffing indicative of fibrotic process. CT may also demonstrate associated ductal plate abnormalities (biliary hamartoma, Caroli disease), and non-hepatic features such as renal abnormalities. On MRI periportal hepatic fibrosis is seen as high signal intensity among portal vessels on T2-w images and especially T2-w half-Fourier acquisition single-shot turbo spin-echo (HASTE) images beautifully depict these tiny proliferating ductules distributed along portal ramifications. MRCP (Ernst et al. 1998) can be utilized to detail the biliary tree, when associated with Caroli disease, and illustrates dilated biliary ducts. Presence of cholangitis may be assessed with post-gadolinium T1-weighted images or regenerative nodules may also be easily characterized.

Differential diagnosis includes cirrhosis due to other causes (alcohol, viral). Features that help discern the differential diagnosis are that the medial segment is normal in size or enlarged in CHF, but is usually small in patients with cirrhosis due to other causes. About complications of this disease, portal hypertension, esophageal varices, HCC (Ghadir et al. 2011), cholangiocarcinoma, amyloidosis, and adenomatous hyperplasia of the liver (Vilgrain et al. 2016) are reported in patients with CHF. Recurrent uncontrolled cholangitis is an indication for liver transplantation.

3.3 Caroli Disease and Caroli Syndrome

Caroli disease was first described by Caroli et al. (1958) as a congenital condition in which the larger (segmental) intrahepatic bile ducts are

dilated. It is a rare complex autosomal recessive congenital disorder characterized by nonobstructive communicating saccular or fusiform dilatations of the large intrahepatic bile ducts. Important associations with Caroli disease include CHF ARPKD (Hussman et al. 1991; Jordon et al. 1989), choledochal cyst (Henry et al. 1987), medullary sponge kidney, and nephronophthisis (medullary cystic kidney disease) (Torra et al. 1997). If the defective remodeling involves the entire intrahepatic biliary tree, Caroli syndrome - CS - (a combination of Caroli disease and CHF) develops. CS is characterized by varying degrees of persistent embryonic bile duct structures, fibrosis, and ductal dilatation. In addition, Caroli disease and CS have also been associated with other hepatorenal fibrocystic diseases including Meckel–Gruber syndrome, cerebellar vermis hypo/aplasia, oligophrenia, ataxia congenital, coloboma, and hepatic fibrosis syndrome (COACH) syndrome, Joubert syndrome and related disorders, Bardet–Biedl syndrome, and oral–facial–digital syndrome. Caroli disease is very rare, with 1 case per 1,000,000 people (Freidman et al. 2007). The liver may be diffusely affected, or the ductal abnormalities more frequently may be localized to one segment or lobe, most commonly the left lobe (Boyle et al. 1989), and in any case less than 50% of the hepatic surface. The pathogenesis of Caroli disease is related to a partial or complete arrest of remodeling of the ductal plate of the large intrahepatic bile ducts (Desmet 1992). The molecular pathogenesis of Caroli disease and syndrome is incompletely understood. The dilated ducts are lined by biliary epithelium that may be hyperplastic and ulcerated. The age of presentation ranges from infants to young adults. About symptoms of Caroli disease the saccular or fusiform dilatation of bile ducts predisposes to stagnation of bile leading to the formation of biliary sludge, intraductal lithiasis, and bacterial cholangitis that may be complicated by septicemia and hepatic abscess formation. Other symptoms include abdominal pain from bile stasis or passage of stones, fever, and right upper quadrant pain when cholangitis is present (Murray-Lyon et al. 1972), which can present with fever and right upper quadrant pain. Jaundice is rarely present in these patients. Secondary biliary cirrhosis can occur due to biliary obstruction. Patients with CS can present with portal hypertension and its sequelae, ascites, and esophageal variceal hemorrhage. Pruritus and hepatomegaly are common. Children with CS usually have an earlier onset of symptoms and a more rapidly progressive disease because of the combined effects of cholangitis and portal hypertension. Caroli disease is a risk factor for malignancy, as neoplastic changes occur in 7% of patients (Arcement et al. 2000).

On US, Caroli's disease appears as well-defined intrahepatic cystic anechoic lesions and calculi or sludge within these cystic areas may increase the echogenicity and may also appear heterogeneous (Marchal et al. 1986). Similarly, contrast-enhanced CT and MRI demonstrate intrahepatic saccular or fusiform cystic areas with sizes measuring up to 5 cm, which often contains calculi and sludge. Peculiar sign is "the central dot sign" fibrovascular bundle lying centrally within the dilated duct that contains a portal vein radically that enhances with contrast (seen as hyper-enhancing or hyperintense focus), (Choi et al. 1990). On MRCP (Figs. 8 and 9) these cystic areas are seen communicating with the bile ducts and it is useful for demonstrating the characteristic features of saccular dilated, non-obstructed, intrahepatic bile ducts that communicate with the biliary tree (Brancatelli et al. 2005). The main differential consideration includes primary sclerosing cholangitis, polycystic liver disease (Fig. 10), and recurrent pyogenic cholangitis. Complications (Miller et al. 1995) are usually a consequence of bile stasis predisposing to recurrent cholangitis, abscess formation, biliary cirrhosis, and occasionally cholangiocarcinoma.

3.4 Choledochal Cyst

Choledochal cysts (Fig. 11) are a congenital dilatation of the extrahepatic and/or intrahepatic bile ducts. Choledochal cysts are classified into five

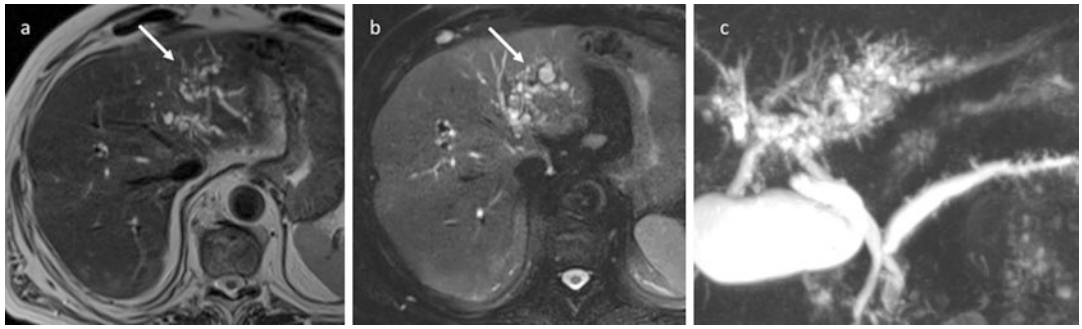

Fig. 8 Caroli disease. (**a**) TSE T2-weighted MRI sequence; (**b**) fat-saturated TSE T2-weighted MRI sequence; (**c**) MR cholangiography. Left liver lobe cystic lesions (arrows) connected with the intrahepatic biliary tree

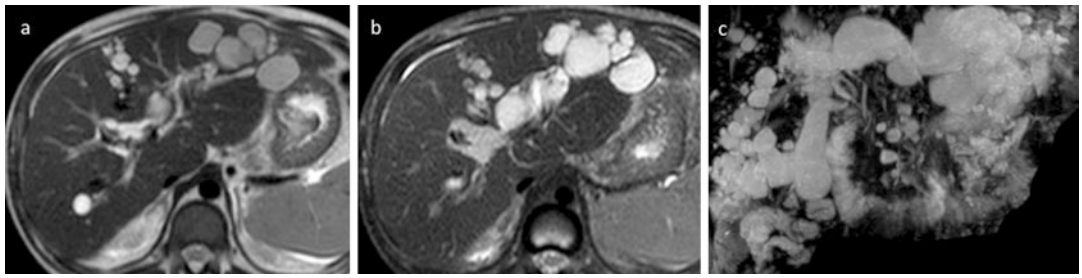

Fig. 9 Caroli disease. (**a**) TSE T2-weighted MRI sequence; (**b**) fat-saturated TSE T2-weighted MRI sequence; (**c**) MR cholangiography. Right and left liver lobe cystic lesions (arrows) connected with the intrahepatic biliary tree

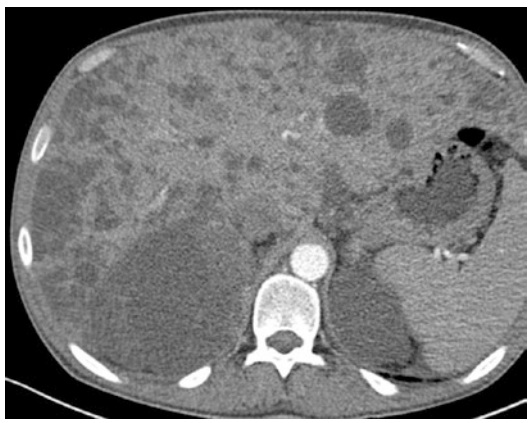

Fig. 10 Polycystic liver disease. Contrast-enhanced CT. Multiple cystic lesions with variable sizes on both liver segments

types based on the Todani modification of the Alonso-Lej classification (Lenriot et al. 1998).

Type I cystic (Ia), segmental (Ib), or fusiform (Ic) dilation of the common bile duct, as well as part or all of the common hepatic duct and extrahepatic portions of the left and right hepatic ducts: A further group (Id, not represented) has been suggested with multiple extrahepatic cysts. Differentiation between the fusiform type and dilation of the bile duct secondary to obstruction is based on the absence of a previous history of gallstones or biliary surgery, a common bile duct diameter >30 mm, and presence of an anomalous bile duct junction shown on cholangiography (Lipsett et al. 1994). Type Ia cysts are associated with abnormal pancreaticobiliary junction and the cystic duct and gallbladder arise from the dilated common bile duct. Type Ib is segmental dilation of an extrahepatic bile duct, often the distal common bile duct. Type Ic is dilation of all the extrahepatic bile ducts and dilation extends from the pancreatobiliary junction, that is anomalous, to the extrahepatic portions of the left and right hepatic ducts. Type Id is cystic dilation of the common duct and cystic duct. This group accounts for 50–85% of all bile duct cysts.

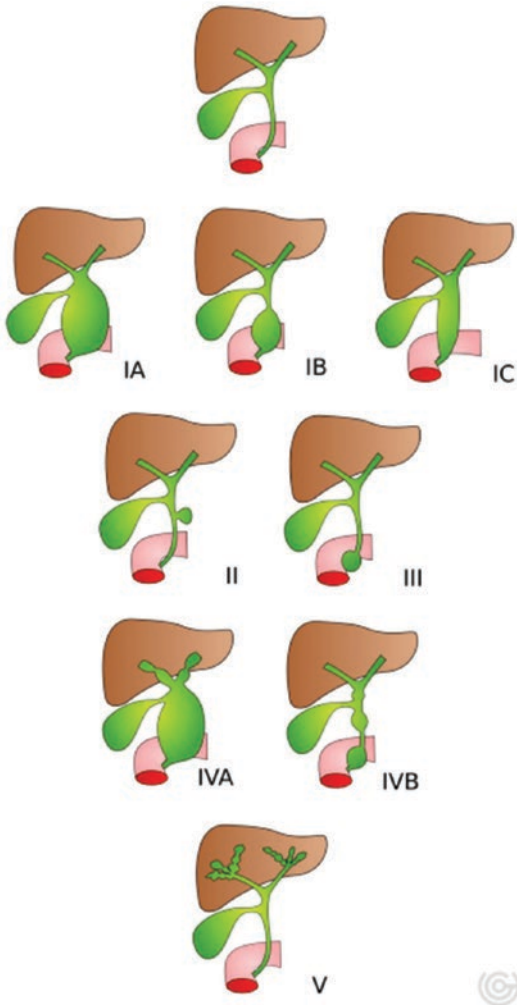

Fig. 11 Classification of choledochal cysts according to Todani modification of the Alonso-Lej classification

Type II cyst forms a diverticulum from the extrahepatic bile duct. It accounts for 2–3% of a bile duct cyst. It represents a true diverticulum. Saccular outpouching arises from the supraduodenal extrahepatic bile duct or the intrahepatic bile ducts.

Type III is cystic dilation (choledochocele) of the distal common bile duct lying mostly within the duodenal wall; it may arise embryologically as duodenal duplications involving the ampulla. It accounts for 1–5% of a bile duct cyst.

Type IV cysts are defined by the presence of multiple cysts and are subdivided based on their intrahepatic bile duct involvement: Type IVa shows intrahepatic and extrahepatic cystic dilations with a distinct change in duct caliber and/or a stricture at the hilum, features that help differentiate it from a type Ic cyst. Type IVb presents multiple extrahepatic cysts but no intrahepatic cysts. It is the second most common type of bile duct cyst (10%).

Type V is characterized by one or more cystic dilations of the intrahepatic ducts, without extrahepatic duct disease known as Caroli disease. It accounts for 1–5% of a bile duct cyst.

Choledochal cyst is more commonly seen in East Asian populations, with a female-to-male ratio of approximately 3.5:1 (Lipsett and Pitt 2003). The majority of patients (60%) are diagnosed before the age of 10 years but the disease can be diagnosed at any age (Sela-Herman and Scharschmidt 1996). Choledochal cysts may be an acquired condition thought to arise from an abnormal pancreaticobiliary junction. Cysts may be congenital or acquired and have been associated with a variety of anatomic abnormalities.

The clinical features include right upper quadrant mass, jaundice (more commonly seen in children), and signs and symptoms of cholangitis (more commonly seen in adults). Choledochal cysts vary in size and may contain as much as 10 L of bile. Microscopically, the cyst wall is fibrotic, thickened (in contrast to simple hepatic cyst which has a thin wall), and chronically inflamed. Bile can be seen within the wall. The epithelial lining of the cyst is usually denuded. When preserved, the lining consists of columnar epithelial cells. Intestinal metaplasia with abundant mucinous glands is a feature which is seen in almost all patients older than 15 years. Affected individuals have an increased risk of developing cholangiocarcinoma that increases with age (Nonomura et al. 1994).

About imaging at US, they appear as anechoic or hypoechoic fusiform or cystic lesions in the porta hepatis, which demonstrate communication with the biliary tree. The dilatated system may demonstrate echogenic sludge or stones. Transabdominal US has a sensitivity of 71–97% for diagnosing biliary cysts (Fulcher et al. 2001). Factors that may limit the usefulness of an

US include the patient's body habitus and the presence of bowel gas that may limit visualization. CT and MRCP offer a noninvasive and accurate diagnosis. CT can detect all types of biliary cysts. It can demonstrate continuity of the cyst with the biliary tree and examine the relationship of the cyst to surrounding structures; it is useful for evaluating the presence of malignancy or for determining the extent of intrahepatic disease in patients with type IVA or V cysts. CT cholangiography with the usage of hepatobiliary excreted iodinated contrast (e.g. Meglumine iodoxamic acid) has been used in the past to delineate the anatomy of the biliary tree with high sensitivity (93%), but its sensitivity (64%) for imaging the pancreatic duct and for pancreatobiliary junction is poor (Lam et al. 1999). MRCP is considered the current gold standard for initial evaluation and diagnosis of choledochal cysts. MRCP techniques are able to accurately assess intra- and extrahepatic biliary anatomy and the pancreaticobiliary junction, and look for associated complications (Guo et al. 2012). On heavily T2-w sequences they are characterized by a hyperintense tubular, fusiform, or cystic structure. However, the detection of intraductal stones may be difficult on this sequence as the protein plugs commonly seen in the cysts are isointense to calculi and differentiation between the two is difficult. Hepatobiliary MR contrast agents allow for better visualization of the bile ducts (Figs. 12, 13, 14, and 15). Alternatively ERCP (Irie et al. 1998) can be used for diagnosis, but it is invasive and is associated with the risk of introducing infection into the dilated biliary system. It has a sensitivity of up to 100% for diagnosing biliary cysts (Keil et al. 2010).

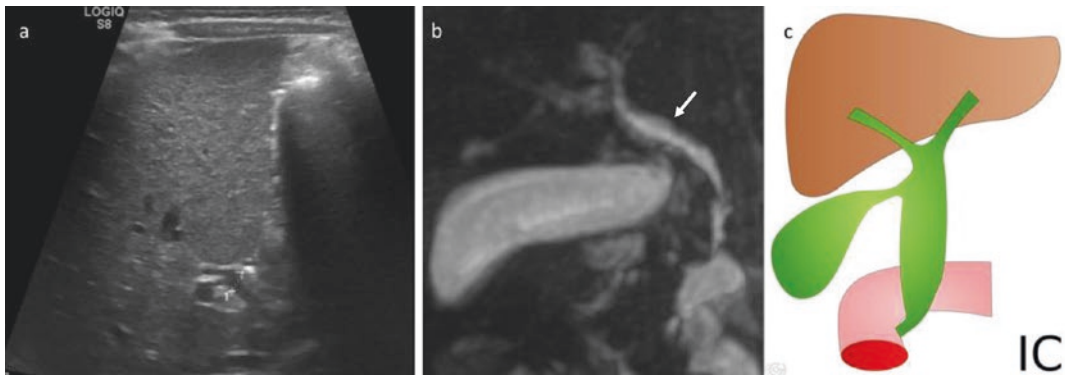

Fig. 12 Type IC choledochal cyst in a boy. (**a**) Transverse US and (**b**) MRCP image shows fusiform dilatation of the common bile duct (arrow) as shown in the scheme (**c**)

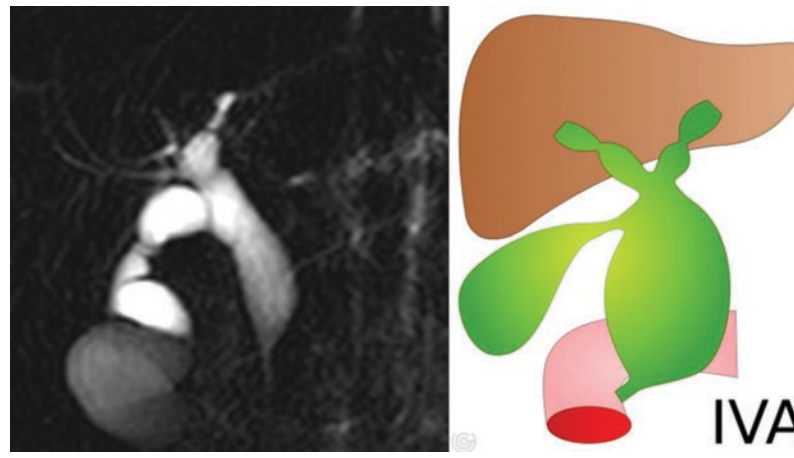

Fig. 13 Type IVa choledochal cyst MRCP image shows fusiform dilatation of the common bile duct and the intrahepatic bile duct

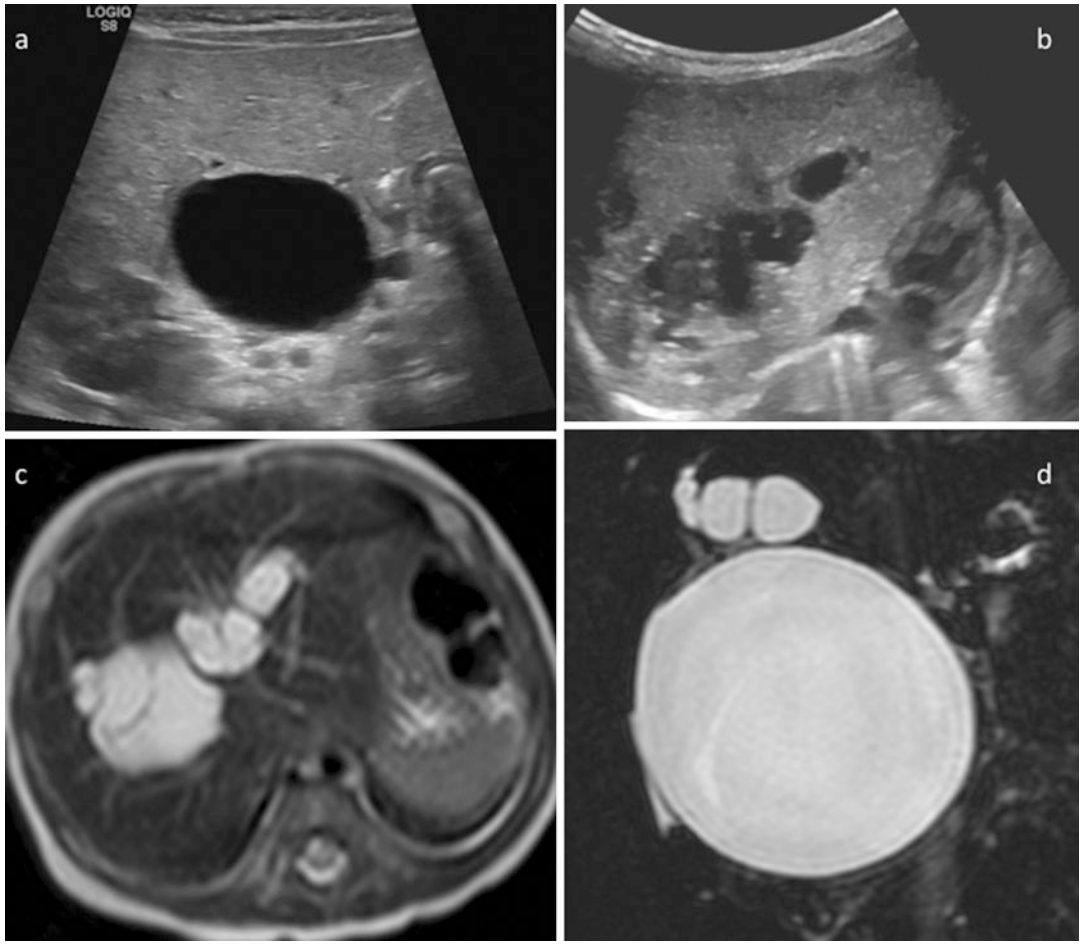

Fig. 14 Type IVa choledochal cyst: massive choledochal cyst on grayscale US (**a**) and (**b**), and on TSE T2-w MRI sequence axial (**c**) and coronal (**d**) planes, in a newborn with evidence of dilation of the common bile duct and intrahepatic bile duct

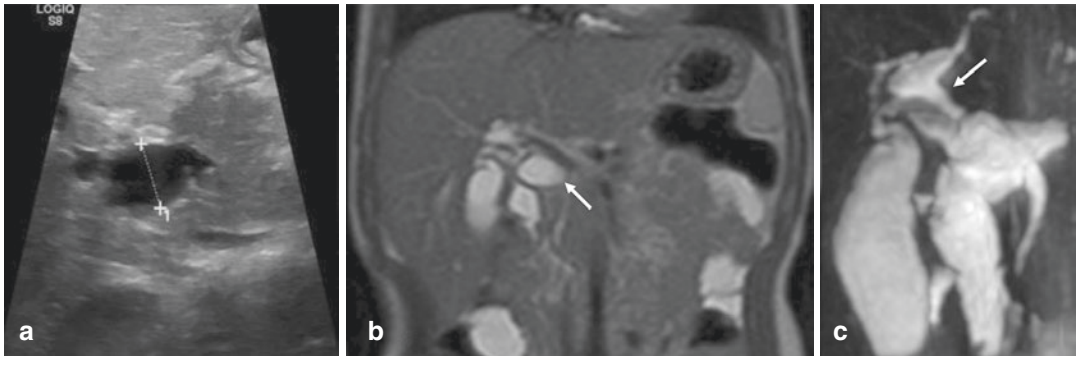

Fig. 15 Type IVa choledochal cyst US (**a**) and MRCP cholangiography images show dilatation of the common bile duct (arrow) (**b**) with evidence of the left intrahepatic bile duct (arrow) (**c**)

Biliary cysts should be differentiated from cysts that do not communicate with the biliary tree including pancreatic, mesenteric, and hepatic cysts and if doubt remains after cross-sectional imaging, hepatobiliary scintigraphy or endoscopic retrograde cholangiopancreatography (ERCP) can be performed to confirm that the cyst communicates with the biliary tree.

Choledochal cysts can be complicated by recurrent cholangitis, pancreatitis, cystolithiasis, and gallstones (70%) (Söreide et al. 2004).

4 Biliary Atresia

Also for this last paragraph, it is good to remember some notions of embryology of the liver (chap. 1 "Embryology and Development of the Liver") before reviewing the characteristics of diseases, biliary atresia (BA), and Alagille' syndrome (AGS).

Biliary atresia (BA) is a progressive, idiopathic, and severe neonatal disease caused by an inflammatory and fibrotic obliteration of the extrahepatic biliary tree. It results in cholestasis and progressive hepatic failure. BA occurs in 1 in 8000–18,000 live births and appears to be more frequent in Asians (Lin et al. 2011) and Africans than Europeans; it occurs in 1 in 15,000 live births in the United States (Hopkins et al. 2017) and it is more common in female than male children. Although the overall incidence is low, BA is the most common cause of neonatal jaundice for which surgery is indicated and the most common indication for liver transplantation in children because BA remains the most common cause of end-stage cirrhosis in children.

The possibility of BA is suggested by the clinical presentation of neonatal jaundice (Makin et al. 2009) and/or acholic stools. After the first 2 weeks of life, acholic stools and conjugated hyperbilirubinemia (cholestasis) must suggest BA as it represents 30–40% of the causes of biliary jaundice. BA is divided into three distinct clinical forms (Hartley et al. 2009) with different etiologic subgroups:

- BA without any other anomalies or malformations (isolated form 80% of patients): This pattern is sometimes referred to as "perinatal" BA, and (Schwarz et al. 2013) typically, these children are born without jaundice, but within the first 2 months of life, jaundice develops and stools become progressively acholic.
- BA in association with other congenital malformations (non-laterality defect, 5–10% of patients) is associated with major cardiovascular, gastrointestinal, and genitourinary malformations that include intestinal atresia, imperforate anus, kidney anomalies, and/or heart malformations (Schwarz et al. 2013) or chromosomal abnormalities such as trisomy 18, trisomy 21, or Turner syndrome.
- BA in association with laterality malformations (1–10% of patients): This pattern is also known as biliary atresia splenic malformation (BASM) or "embryonal" BA (Davenport et al. 1993). The laterality malformations include situs inversus, asplenia or polysplenia, intestinal malrotation, interrupted inferior vena cava, preduodenal portal vein, and cardiac anomalies.

In addition, cystic dilatation of biliary remnants may be seen in a small minority of cases of embryonal type biliary atresia (approximately 8% of cases); another variant is BA associated with cytomegalovirus (CMV) (Zani et al. 2015).

Several surgical classifications of BA have been proposed, for example Kasai classification (Kasai et al. 1976) that distinguishes type I (the common bile duct is obliterated while the proximal bile ducts are patent); type IIa (atresia of the hepatic duct, the cystic and common bile ducts are patent); type IIb (the cystic, common bile, and hepatic ducts are obliterated); and type III (atresia refers to discontinuity of the right and left hepatic ducts to the level of the porta hepatis, more than 90% of cases) (Fig. 16).

The pathogenesis of BA is incompletely understood but appears to be multifactorial; the genetic factors driving this inflammatory process and the molecular basis of phenotypic heteroge-

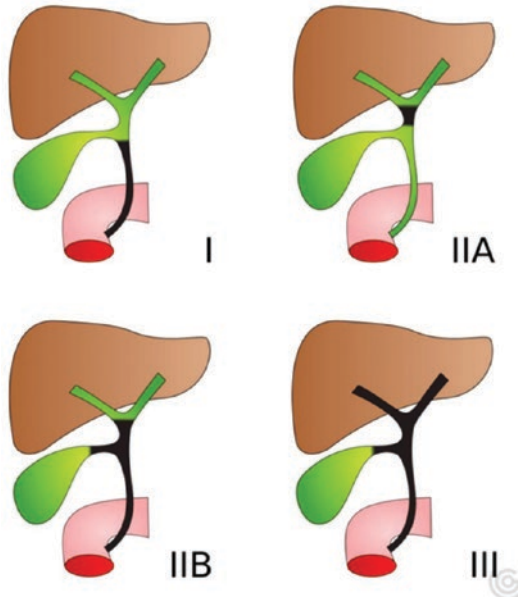

Fig. 16 Schematic illustration of biliary atresia

neity in affected infants remain undefined and many factors have been incriminated. Some of them may be related to a defect in early bile duct development (mainly observed in patients with several abnormalities) and some may arise during perinatal period, due to external factors, such as cytomegalovirus (Zani et al. 2015), reovirus (Szavay et al. 2002), rotavirus, environmental toxins and neonatal immune dysregulation. A possible association of congenital malformation with deletion of the gene GPC1, which is located on the longarm of chromosome 2 (2q37) (Al-Salem 2014)* and is usually responsible for identification of active and progressive inflammation, have been implicated in the pathogenesis of BA and early destruction of the biliary system. Finally, a definitive pathogenesis of BA remains uncertain.

After birth, most infants with BA are born at full term; the clinical triad of BA is jaundice (conjugated hyperbilirubinemia lasting beyond 2 weeks of life) (Wang 2015), acholic (white) stools, and dark urine, hepatosplenomegaly.

The first imaging examination to which the newborn is subjected is the US with the aim of evaluating the biliary tract and in the first instance to exclude other anatomical causes of cholestasis. US evaluates the presence of liver masses, biliary ductal dilatation, choledochal cysts, vascular anomalies, signs of portal hypertension, and polysplenia. On US, furthermore, reduced gallbladder size (<15 mm) (Aziz et al. 2011) and shape (shrunk despite fasting), "triangular cord" sign (liver hilum, in the vicinity of the portal vein, appearing hyperechoic with thickness >4 mm) (So Mi Lee et al. 2015), gallbladder reduced contractility, and absence of the common bile duct can be suggestive of BA (Zhou et al. 2016). For evaluation of gallbladder contraction, the examination is repeated 60–90 min after the infant was fed. The volume of gallbladder is calculated using $V = 0.52 \times \text{width} \times \text{width} \times \text{length}$. A diameter of the hepatic artery larger than 1.5 mm is considered as hepatic artery enlargement and it shows a sensitivity of 92%, a specificity of 87%, and an accuracy of 89% in the diagnosis of BA (Kim et al. 2007). In syndromic BA infants, US may show other features such as multiple spleens, preduodenal portal vein, absence of retrohepatic IVC, or abdominal situs inversus (Schwarz et al. 2013).

MRCP may be useful for the evaluation of the patency of intra- and extrahepatic biliary tree with reported diagnostic accuracy of 71–82% (Yang et al. 2009).

If no diagnosis emerges from the initial laboratory or imaging studies, hepatobiliary scintigraphy with a variety of 99mTc labelled iminodiacetic acid (IDA) agents is diagnostic imaging study that can be used to assess hepatocellular function and patency of the biliary system by tracing bile flow from the liver through the biliary system into the bowel. A lack of excretion of bile into the bowel is suggestive of extrahepatic occlusive disorders including BA (Kianifar et al. 2013). In case of failure to diagnose or when the gallbladder seems normal on US, cholangiography is needed to assess the morphology and patency of the biliary tree. Direct imaging of the biliary tree by cholangiography is performed either percutaneously (puncture of the gallbladder) (Lee et al. 2011) or endoscopically (ERCP) (Shanmugam et al. 2009). These procedures are invasive; however demonstration of a patent extrahepatic biliary tree effectively

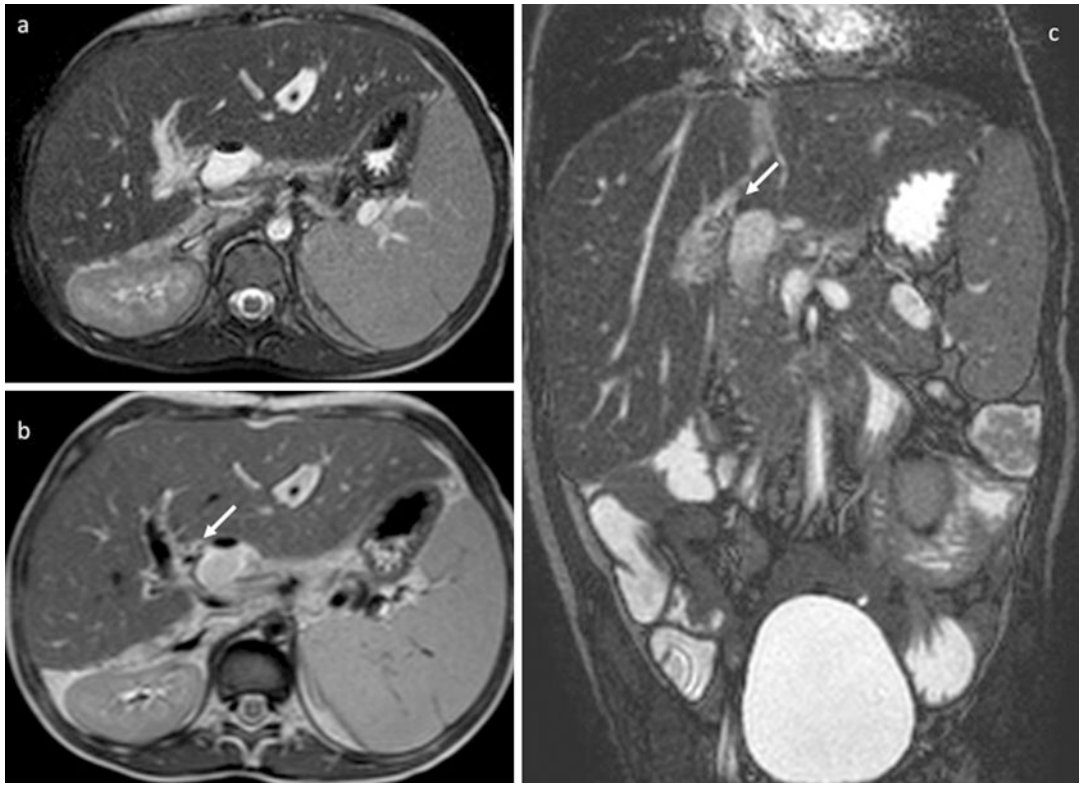

Fig. 17 Kasai portoenterostomy in a female with biliary atresia. TSE T2-w MRI sequences on transverse (**a**, **b**) and coronal planes (**c**)

excludes biliary atresia. At liver biopsy the main histopathologic features of BA are portal tracts with bile duct proliferation, portal tract edema, fibrosis and inflammation, and canalicular and bile duct bile plugs; the portal tracts are expanded by edema, neutrophilic infiltrate, and a prominent periportal ductular reaction (Kahn 2004). Portal fibrosis is progressive and the severity depends on the age at diagnosis and the duration of ductal obstruction. About 15% of cases show giant cell transformation of hepatocytes (Hussein et al. 2005). If BA is confirmed, Kasai hepatic portoenterostomy (HPE) is performed in the first months of life, in which the extrahepatic biliary system is surgically removed and replaced with a loop of intestine (Roux-en-Y anastomosis) that is connected directly to the portal area of the liver (Kasai and Suzuki 1959); it allows the restoration of bile flow and relief of obstruction (Fig. 17). The alternative is liver transplantation, when the patients develop ascending cholangitis, progressive biliary cirrhosis, portal hypertension, esophageal varices, and ascites (Shneider et al. 2012). With the combination of HPE and liver transplantation, most children with BA now survive into adulthood (Hartley et al. 2009). About differential diagnosis, causes of neonatal cholestasis, such as Alagille syndrome, alpha-1-antitrypsin deficiency, sclerosing cholangitis with neonatal onset, and cystic fibrosis, must be excluded.

4.1 Alagille Syndrome

Alagille syndrome (AGS), also known as arteriohepatic dysplasia, is a complex, multisystemic, and an autosomal dominant disorder characterized by ductopenia (paucity of intrahepatic bile ducts) that causes cholestasis, in association with a wide range of extrahepatic subdivided into four

main clinical abnormalities (Spinner et al. 2013): cardiac disease, skeletal abnormalities, ocular abnormalities, and characteristic facial features. This multisystem condition has an estimated frequency of 1 in 30,000 (Piccoli and Spinner 2001) and this disorder is localized to defects in the Notch signaling pathways: up to 98% are caused by mutations in JAG1, gene on chromosome 20p12, and 2% are caused by mutations in Notch-2 receptor, gene variant of unknown significance (Brennan and Kesavan 2017). JAG1 is a ligand of the Notch receptors; in turn the Notch activated by Jag1 plays a vital role in the regulation of cell differentiation, thereby controlling neurogenesis, hematopoiesis, myogenesis, somitogenesis, endocrinogenesis, and adipogenesis (Turnpenny and Ellard 2012). Disruption of the JAG1/Notch sequence leads to embryonic developmental abnormalities of many organs. Notch signaling has been shown to be essential in the development of the biliary tree during ductal plate remodeling because *JAG1* gene leads to overexpression of the hepatocyte growth factor (HGF) and that is thought to result in increased differentiation of the hepatic stem cells to hepatocytes and less to biliary cells, thus causing bile duct paucity. Of note, alteration in the expression of *JAG1* and Notch has also been reported in the course of chronic liver diseases (Fabris et al. 2007).

The hepatic phenotype is recognized by variable degrees of cholestasis, jaundice, and pruritus. Fibrosis is not a main feature of AGS and evolution to cirrhosis is rare; however in approximately 15% of cases it leads to liver transplantation (Emerick et al. 1999). In newborns with AGS, bile duct paucity is not always present and liver biopsy may demonstrate ductal proliferation portal inflammation, which may lead to a misdiagnosis of biliary atresia, and this is important because BA patients may undergo the Kasai procedure, which is not beneficial in AGS (Kaye et al. 2010); in late infancy and early childhood bile duct paucity appears to be progressive. Xanthomas, fatty deposits on the extensor surfaces, and failure to thrive due to fat malabsorption may also be there (Mouzaki et al. 2015). A small proportion of patients have no manifestations of liver disease.

About cardiac disease pulmonary vasculature is the most commonly involved. Peripheral pulmonary stenosis is the most common cardiac finding and the most common complex cardiac defect is tetralogy of Fallot; other cardiac malformations include ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta (Emerick et al. 1999).

The most common skeletal abnormalities are butterfly-shaped thoracic vertebrae, secondary to clefting abnormality of the vertebral bodies, narrowing of the interpedicular distance in the lumbar spine, pointed anterior process of C1, spina bifida occulta, and fusion of adjacent vertebrae and hemivertebrae, and absence of the 12th rib, a square shape of the proximal part of the fingers with tapering distal phalanges and extra digital flexion creases (Turnpenny et al. 2007). There may be an increase in pathological long-bone fractures in AGS, which may be due to cholestasis and/or an intrinsic defect of the bones.

Ocular abnormalities in individuals with AGS are posterior embryotoxon (a prominent Schwalbe's ring), a defect in the anterior chamber of the eye (Hingorani et al. 1999), and Axenfeld-Rieger anomaly, which is characterized by an abnormal pupil that is off-center (corectopia) or by extra holes in the iris that look like multiple pupils (polycoria). Other manifestations are microcornea, keratoconus, congenital macular dystrophy, shallow anterior chamber, exotropia, band keratopathy, and cataracts; diffuse hypopigmentation of the retinal fundus may occur.

Characteristic facial features are dysmorphic facies, broad forehead, deep-set eyes sometimes with upslanting palpebral fissures, prominent ears, straight nose with bulbous tip, and pointed chin giving the face a somewhat inverted triangular appearance (McDaniell et al. 2006).

Generally major criteria for diagnosis are considered as butterfly vertebrae, characteristic facies, and ocular abnormalities. Minor criteria include vascular accidents, intracranial bleeding, renal anomalies, xanthomas, supernumerary digital flexion creases, hypothyroidism, growth hormone insensitivity, pancreatic insufficiency, failure to thrive, growth retardation, and intellec-

tual disability. Genetic test is mandatory for diagnosis.

As AGS is a multisystem disorder with a wide spectrum of clinical variability ranging from life-threatening liver or cardiac disease to only subclinical manifestations, such as mildly abnormal liver enzymes, a heart murmur, butterfly vertebrae, posterior embryotoxon, or characteristic facial features or neurovascular malformation, the diagnosis may be difficult because of the variable expressivity of the clinical manifestations. X-ray is useful for evaluation vertebrae. US, scintigraphy, and MRCP may be useful for evaluation of the patency of intra- and extrahepatic biliary tree (Yang et al. 2009). Definitive diagnosis of AGS about liver requires biopsy-proven paucity of interlobular bile ducts. US is useful for evaluation of hepatic masses (Fig. 18) and for evaluation of kidneys for structural problems such as small kidney, unilateral and bilateral multicystic kidney, dysplastic kidneys, horseshoe kidneys, and ureteropelvic obstruction (McDaniell et al. 2006). Cerebral vasculopathy is an important feature of AGS and includes dolichoectasia, cerebral aneurysms, and moyamoya arteriopathy (progressive intracranial arterial occlusive showed "puff-of-smoke" appearance in DSA) (Connor et al. 2002). In the event of a serious head injury or neurological symptom, it is mandatory to aggressively and rapidly evaluate these children clinically and with appropriate imaging CT, MRI, and angiography (Doberentz et al. 2015). MRI screening in these patients is not validated yet. In addition to cerebral arterial abnormalities, alterations of venous development may be a feature of AGS in adults.

As for therapy, the severity and presentation of AGS determine the level of treatment, ranging from supportive care to standard medical management for cardiac and hepatic complications, including transplantation and cardiac surgeries in severe cases (Spinner et al. 2013). Prognosis of

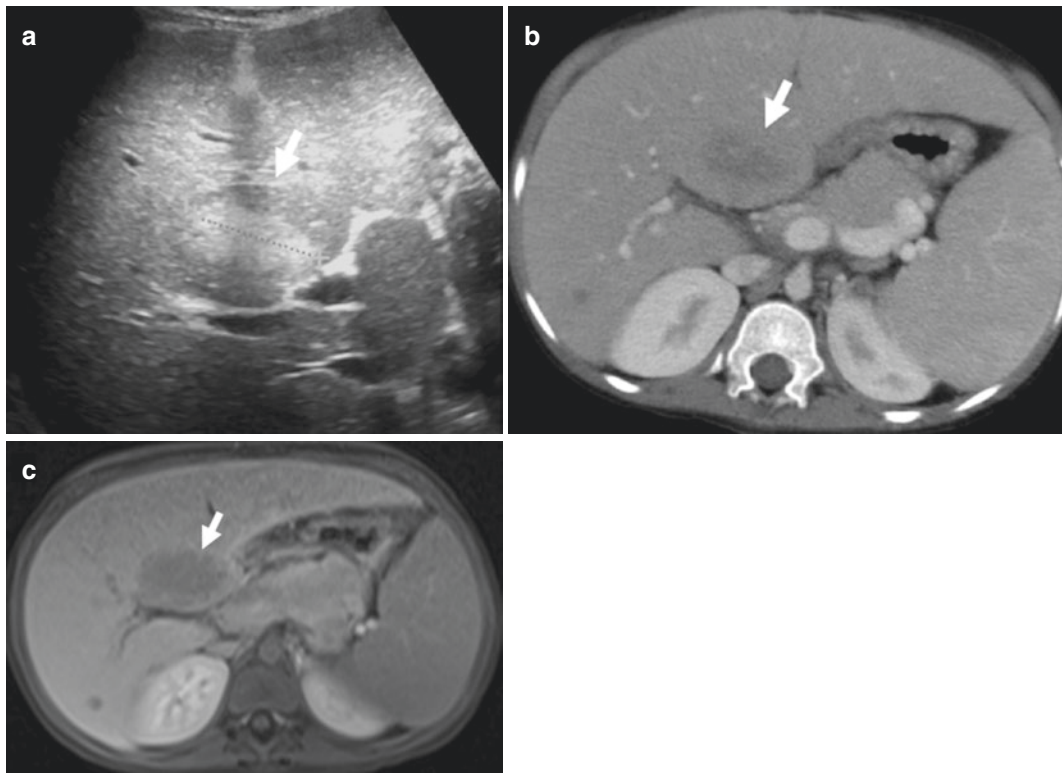

Fig. 18 Regenerative hepatic nodule (arrow) in the fourth hepatic segment on US (**a**), contrast-enhanced CT (**b**), and MRI (**c**) in a female 12-year-old with Alagille syndrome

AGS is also related to severity of organ involvement, with congenital heart disease, progressive liver disease, intracranial bleeding, and infection being the main contributors to increased mortality.

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