PICTORIAL REVIEW

Hepatobiliary anomalies associated with *ABCB4*/MDR3 deficiency in adults: a pictorial essay

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Abstract

Background ABCB4/MDR3 gene variants are mostly associated with a peculiar form of cholelithiasis in European adults, currently referred to as low phospholipid-associated cholelithiasis (LPAC) syndrome.

Methods LPAC syndrome is a rare genetic disorder, characterised by the following clinical features: biliary symptoms before the age of 40, recurrence of the symptoms after cholecystectomy, and intrahepatic microlithiasis or intrahepatic hyperechogenic foci.

Results Imaging features associated with ABCB4/MDR3 mutations are not specific and correspond to a wide spectrum of biliary abnormalities. The main feature is the presence of intrahepatic lithiasis. Other uncommon presentations have been described, such as uni- or multifocal spindle-shaped dilatations of the intrahepatic bile ducts filled with gallstones, secondary sclerosing cholangitis, biliary cirrhosis, and intrahepatic cholangiocarcinoma.

Conclusion This review focuses on MR features related to ABCB4/MDR3 mutations.

Main Messages

• *LPAC syndrome is characterised by intrahepatic microlithiasis or intrahepatic hyperechogenic foci.*

• *Ultrasound examination is very accurate in detecting intrahepatic stones.*

• *At MR imaging, LPAC syndrome is associated with various presentations.*

Introduction

In 1996, Deleuze et al. [1] initially suspected the role of defects in the multidrug resistance 3 P-glycoprotein (MDR3) in a subtype of progressive familial intrahepatic cholestasis (PFIC). This refers to a heterogeneous group of familial cholestatic conditions caused by defects in biliary epithelial transporters. The disease usually occurs first in childhood with progressive cholestasis leading to death from liver failure at ages ranging from infancy to adolescence [2]. The underlying genetic and molecular abnormalities related to PFIC have led to the identification of three subtypes and the description of several mutations in hepatocellular transport system genes involved in bile formation. Only PFIC 3 can be related to defects in the *ABCB4* gene encoding MDR3. MDR3 is a phospholipid translocator involved in biliary phosphatidylcholine excretion. The result of these mutations is a reduced amount of phosphatidylcholine in bile. Phosphatidylcholine solubilises cholesterol in mixed micelles and prevents damage to the biliary epithelium from unbound bile acids. The 'unchaperoned' bile acids in the bile of patients with MDR3 deficiency may cause chronic cholangitis. Several other biliary disorders have been associated with *ABCB4*/MDR3 mutations: low phospholipid-associated cholelithiasis (LPAC) syndrome, intrahepatic cholestasis of pregnancy (ICP), drug-induced liver injury, transient neonatal cholestasis [TNC], adult biliary fibrosis or cirrhosis [3], and very recently intrahepatic cholangiocarcinoma (IHCC) [4–9].

In young adults, *ABCB4*/MDR3 alterations are mostly associated with LPAC syndrome and ICP. In the latter case, patients typically present with pruritus that can lead to

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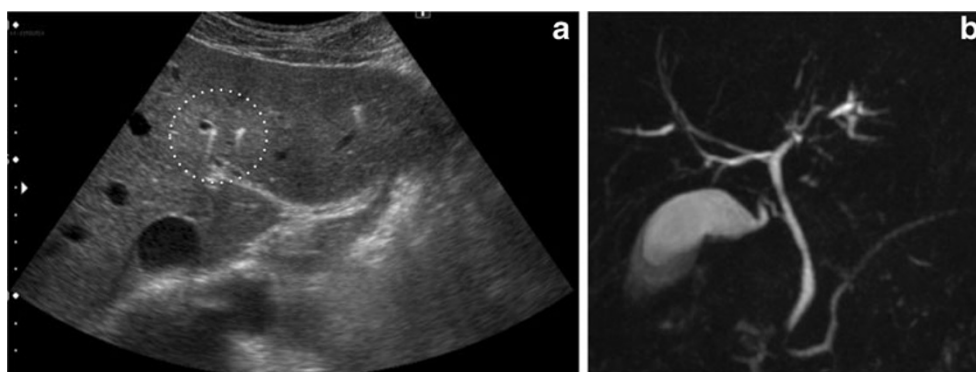
complications for both mother and fetus. In the former case, patients present with intrahepatic biliary lithiasis. The diagnosis of LPAC syndrome is often delayed and relies on clinical and biological elements.

This review will focus on imaging features of hepatobiliary anomalies associated with *ABCB4*/MDR3 deficiency in adults, with special attention to MR characteristics.

Intrahepatic lithiasis

Intrahepatic lithiasis is considered to be very uncommon in Europe and much more frequent in Asia [10]. Since the description of MDR3 deficiencies, an increasing number of patients are diagnosed with LPAC syndrome-related intrahepatic lithiasis. The diagnosis is frequently performed several years after the beginning of the symptoms due to their lack of specificity. The syndrome should be suspected in case of the association of several elements. The three most important are: (1) biliary symptoms in a young adult (<40 years old); (2) symptom recurrence after cholecystectomy; (3) presence of hyperechoic material in the biliary ducts. Other minor criteria have been described, such as mild chronic cholestasis, at least one episode of cholangitis, acute pancreatitis or biliary colic, efficiency of ursodesoxycholic acid (UDCA) and similar symptoms in first-degree relatives. *ABCB4* gene mutations have been described in patients with LPAC syndrome in 25–56 % of cases [11–13]. At imaging, LPAC syndrome is associated with various MR presentations: normal MR cholangiography, isolated intrahepatic lithiasis and, rarely, bile duct dilatations. No imaging differences can be found between patients with or without *ABCB4* mutation and no specific mutation can be associated with the different presentations [12, 14].

The most common presentation of LPAC syndrome is isolated intrahepatic lithiasis. In LPAC patients, most stones are referred to cholesterol "yellow" stones. Cholesterol stones may vary in colour from light-yellow to dark-green or brown. To be classified as such, they must be at least 50 % cholesterol by weight [15] (or 70 %, according to the Japanese classification system) [16, 17]. They may also be calcium bilirubinate

"brown" stones (pigment stones) [18]. Those are traditionally favoured by bile infection, frequent in the Asiatic population but much rarer in western countries.

Ultrasound examination is very accurate in detecting intrahepatic stones, since they appear as heterogeneous and echoic foci centred on the intrahepatic ducts, or as a "comet-
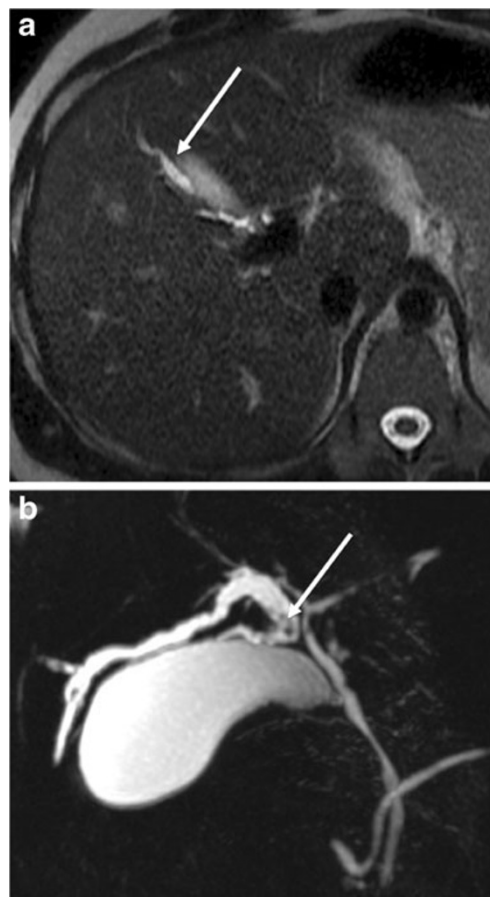

Fig. 2 Unifocal mild biliary dilatation with biliary stone in a 40-year-old man with LPAC syndrome. The dilatation is located in the segment V on T2-weighted acquisitions (*white arrow* in **a**) and 3D MRCP (**b**) and contains a small signal void corresponding to an endoluminal stone (*white arrow* in **b**). The gallbladder and the common bile duct show no abnormalities

tail" artefact due to ultrasound reverberation (Fig 1) [19, 20]. The artefact is not mobile, as opposed to pneumobilia. The "comet-tail" artefact may be due to intrahepatic lithiasis or to the associated cholangiopathy.

If endoscopic retrograde cholangiopancreatography (ERCP) has been considered as the "gold standard" for diagnosing bile duct stone, magnetic resonance cholangiopancreatography (MRCP) is a non-invasive alternative technique that has been shown to be equivalent to ERCP in choledocholithiasis diagnosis and superior to ERCP in intrahepatic lithiasis diagnosis [21–23]. The diagnosis of biliary stone is based on the presence of round or oval shape signal voids in the lumen of the bile ducts on heavily T2-weighted sequences (Figs. 2, 3, 4, 5, 6 and 7). However, it is occasionally difficult to diagnose stones when the surrounding liquid is not present. On T1-weighted sequences, stones present with a spontaneous hyperintensity and, recently, studies have shown the superiority of these sequences over the T2-weighted sequences for the detection of biliary stones [24]. Discrepancies between MR and ultrasound have been reported as MR is not able to detect very small stones (Fig 1), while ultrasound may be suboptimal in case of massive

Fig. 4 Bisegmental dilatation in a 36-year-old woman with LPAC syndrome. Transverse T1-weighted acquisition with fat saturation after injection of a gadolinium chelate at portal phase (**a** and **b**), and 3D MCRP (**c**) show a mild biliary dilatation of both segment III (*white arrow* in **a**) and VI (*white arrow* in **b**). The MRCP shows a round signal void in the dilated bile ducts of the segment III (*white arrow* in **c**) corresponding to a biliary stone
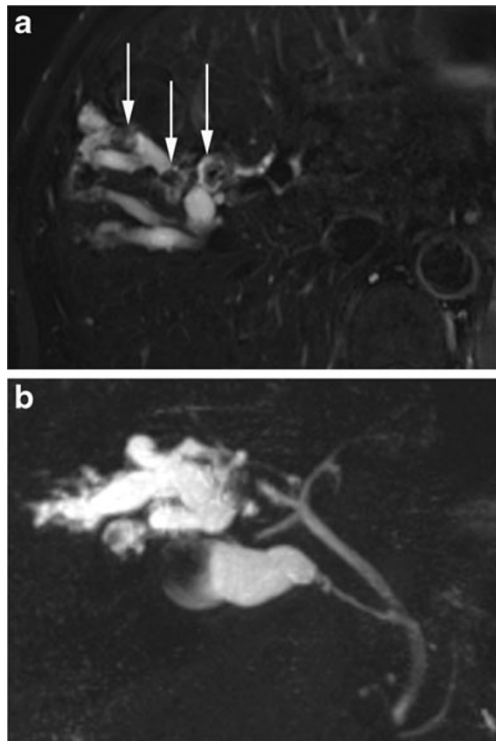

Fig. 3 Severe unisegmental dilatation with endoluminal stones in a 44-year-old woman with LPAC syndrome. Several dilated bile ducts in segment VIII containing macroscopic signal voids corresponding to biliary stones (*white arrows*). **a** Transverse T2-weighted acquisition with fat saturation and (**b**) 3D MCRP

intraluminal stones (Fig 7). A complementary exploration by ultrasound and MR should be recommended.

Computed tomography (CT) performance for the diagnosis of intrahepatic lithiasis depends on the calcium content of bile stones. Cholesterol stones present with a typical hypodense aspect and are poorly visible. MR and ultrasound are superior to CT is such cases.
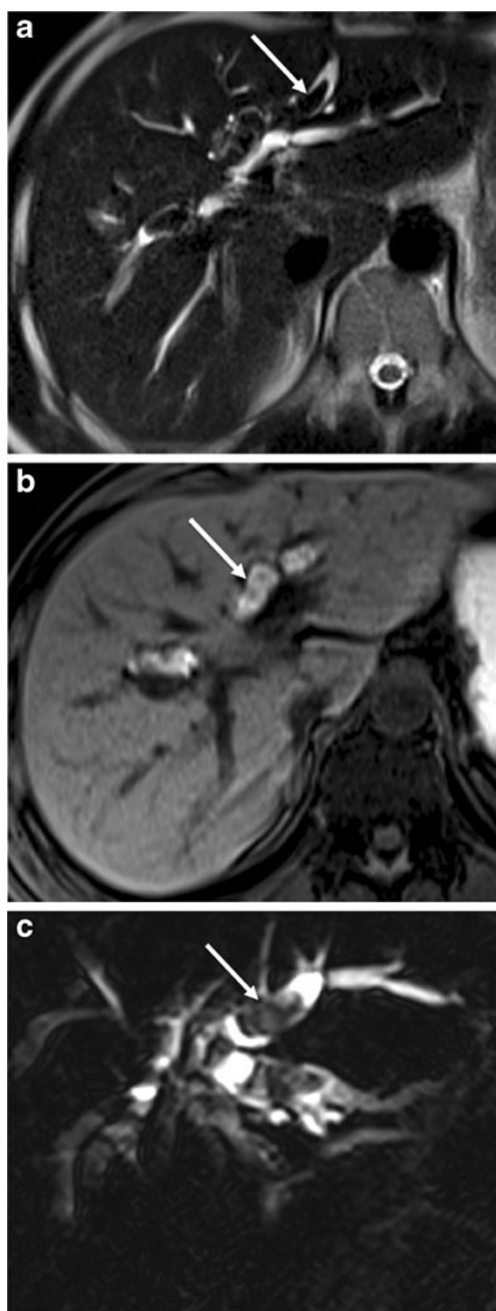
Fig. 5 Diffuse global bile duct abnormalities in a 48-year-old man with LPAC syndrome. Transverse T2-weighted acquisition (**a**), transverse T1-weighted acquisition with fat saturation (**b**), and coronal maximum intensity projection MCRP (**c**) show a biliary dilatation in both right and left lobes containing biliary stones depicted as T2 hypointense and T1 hyperintense endoluminal formations (*white arrow* in **a** and **b**). The MRCP shows large oval shape signal voids in the dilated bile ducts (*white arrow* in **c**) corresponding to biliary stones
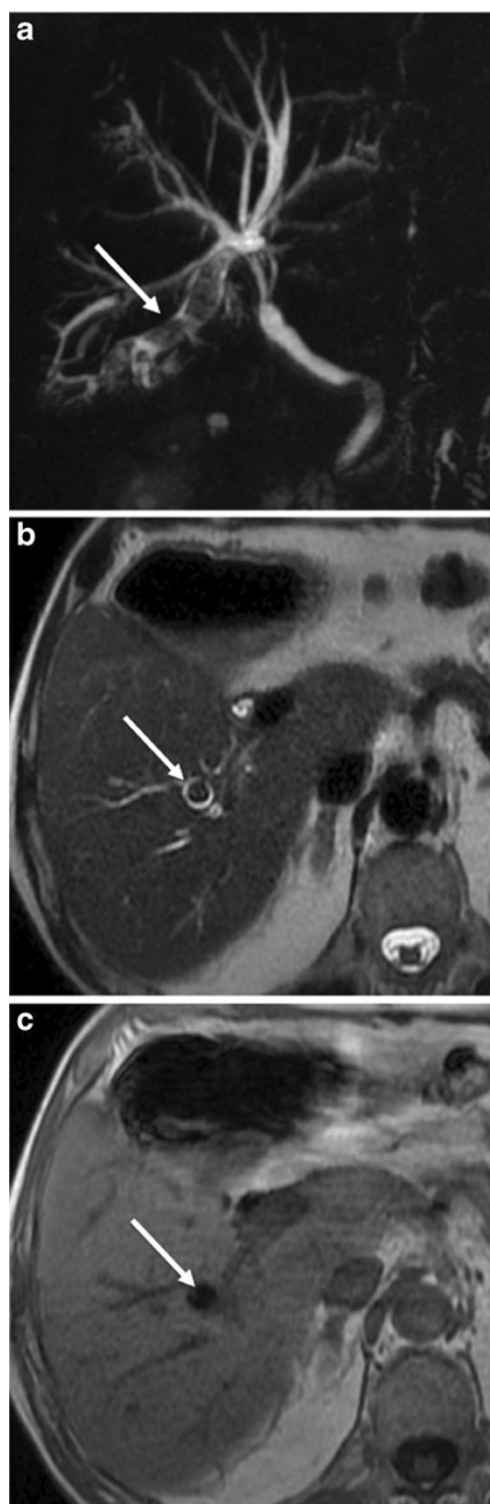
Fig. 6 Segmental dilatation of segment VI bile duct filled with several stones in a 69-year-old man with LPAC syndrome. Coronal maximum intensity projection MCRP (**a**), transverse T2-weighted acquisition (**b**), and transverse in-phase T1-weighted acquisition (**c**) show a dilatation of segment VI bile ducts filled with several stones (*white arrow* in **a**). The stones appear as endoluminal signal voids on T2-weighted acquisition (*white arrow* in **b**) and hypointensities on T1-weighted acquisitions (*white arrow* in **c**)
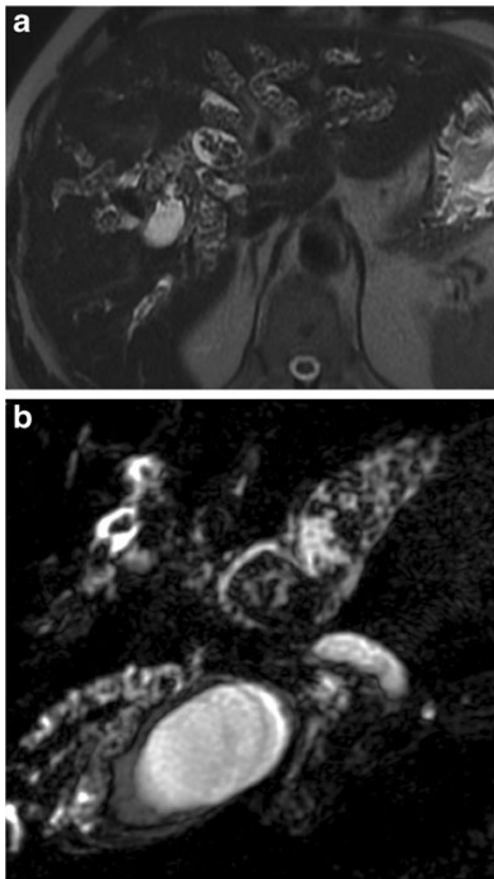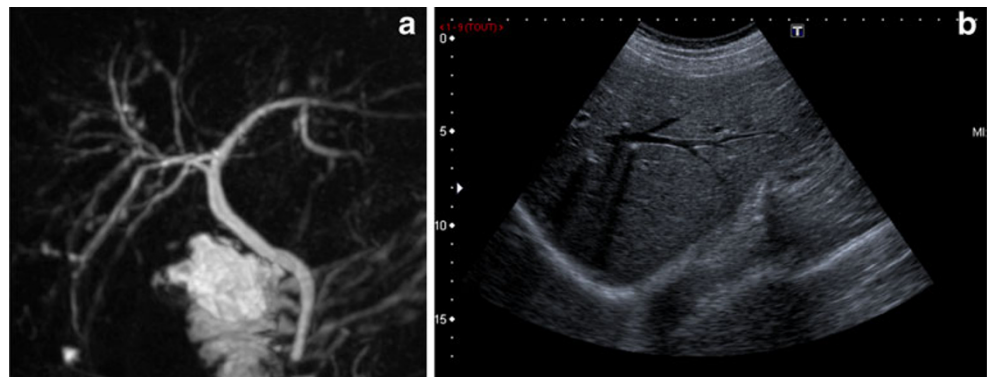
Bile duct dilatations

When bile duct dilatations are present, they appear as mild to moderate. Rarely, patients may present with more severe dilatations (<10 %) [14]. Such severe bile duct dilatation

Fig. 7 Severe LPAC syndrome in a 55-year-old man. Transverse T2-weighted acquisition (**a**), and coronal maximum intensity projection MCRP (**b**) show a rare presentation of severe LPAC syndrome consisting in diffuse biliary dilatation containing multiple biliary stones

may only involve one or two liver segments or may be diffuse (Figs. 3, 4, 5, 6 and 7). In such cases, and as opposed to ductal plate malformations (Caroli disease, congenital hepatic fibrosis, congenital cystic anomalies of the common bile duct, etc.), which are directly related to abnormal embryological development of the bile ducts, abnormalities are related to a biliogenesis disorder developed on initially normal ducts. Anomalies are a consequence of the chronic alteration of the bile composition, which results in damage to the biliary epithelium. Bile duct abnormalities are demonstrated as unifocal or multifocal non-cystic large spindle-shaped bile duct dilatations [14] (Figs. 2, 3, 4, 5, 6 and 7). However, ductal plate malformations, particularly the Caroli disease, have to be ruled out by the absence of specific features, such as the "central dot sign", dilated bile ducts associated with focal area of cystic ectasia, or the fact that no biliary dilatation can be found in LPAC syndrome without underlying biliary stones [14, 25]. Other possible differential diagnosis is bile duct dilatations related to focal obstacle on the biliary ducts. Traditionally, downstream-acquired stenosis (iatrogenic, biliodigestive anastomosis, sclerosing cholangitis, cholangiocarcinoma) may lead to obstructive dilatations that appear more central without intrahepatic lithiasis [14].

Cholangitis

In mice, the multidrug resistance (MDR) glycoproteins that mediate the translocation of phosphatidylcholine across the canalicular membrane of the hepatocyte are called MDR2. Whereas the main feature in MDR2 knock-out mice, which corresponds to the equivalent animal model of human MDR3 deficiency [26, 27], is sclerosing cholangitis, controversies exist whether a genetically determined dysfunction of MDR3 plays a pathogenic role in primary biliary cirrhosis and primary sclerosing cholangitis (PSC) in humans. Pauli-Magnus et al. [28] found no genetic argument supporting the role of MDR3 in PSC. Since then, concepts in PSC understanding have evolved and many authors consider that PSC may represent a mixed bag of diseases of different aetiologies in which several genes such as *ABCB4*/MDR3 may play a disease modifier role [29]. To support this conceptual view, our group recently reported for the first time, in a series of 13 patients with MDR3
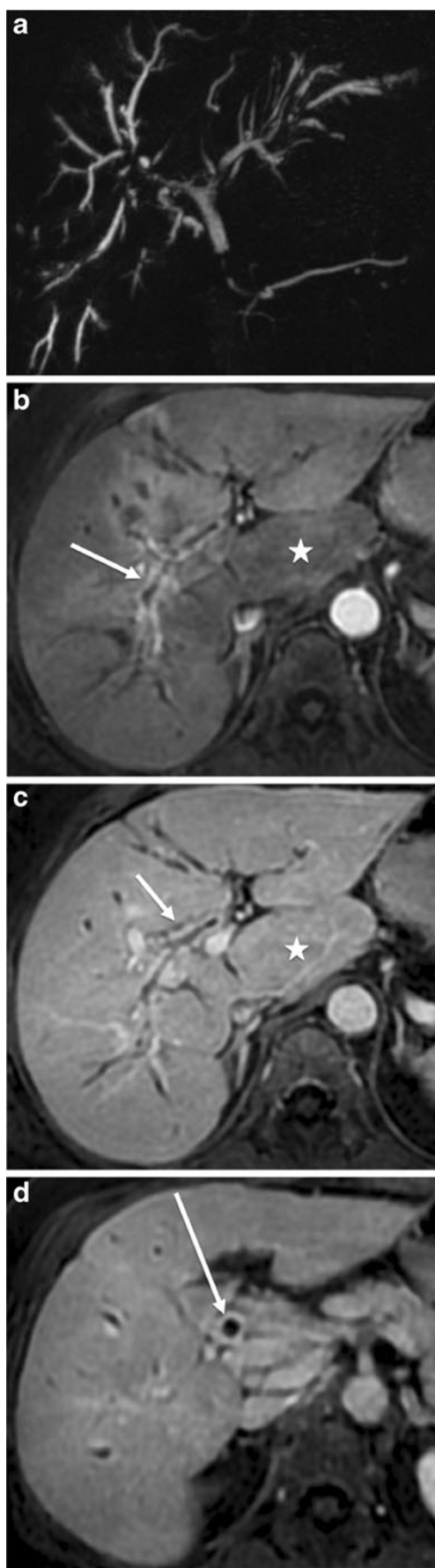
Fig. 8 Biliary irregularities in a 54-year-old man. Three-dimensional MRCP (**a**) and sagittal ultrasound of the right lobe (**b**) show right biliary abnormalities (**a**). These mild irregular calibre intrahepatic bile ducts were not demonstrated with ultrasound; on the other hand, small bile stones were easily depicted as hyperechoic formations with posterior attenuation

deficiency, imaging presentations mimicking sclerosing cholangitis in two patients at MR imaging [30] (Figs. 8 and 9). They corresponded to small duct fibro-obliterative lesions at pathology, and may be due to the direct toxic effect of biliary acids on epithelium. To our knowledge, this is the only report of such association of MDR3 deficiency and secondary sclerosing cholangitis but the two patients presented with recurrent cholangitis and not LPAC syndrome per se.

Complications

All complications associated with chronic cholangitis and/or cholelithiasis have been described in patients with LPAC syndrome: intrahepatic cholangiocarcinoma (IHCC) (Fig. 10), portal hypertension, cholangitis and abscess formation (Fig 11), hepatic fibrosis or cirrhosis. IHCC is a rare primary liver tumour (10-20 %) [31, 32]. Several risk factors have been identified and differ in western and Asian populations: primary sclerosing cholangitis, congenital biliary abnormalities and hepatolithiasis [32]. In most cases, no underlying risk factor is found. Recently, Tougeron et al. [9] reported two cases of IHCC in different and unrelated families with MDR3 deficiency. In both cases, no argument supporting the direct relation between *ABCB4* mutations and tumorigenesis was found and IHCC may be considered as a consequence of the chronic biliary abnormalities. Genetic polymorphisms in biliary transporters genes have been studied but, to date, no relation has been established between IHCC and *ABCB4* mutations [4].

Fig. 10 Severe LPAC syndrome with secondary intrahepatic ▶ cholangiocarcinoma formation in a 55-year-old woman. Maximum intensity projection coronal MRCP (**a**), and transverse T2-weighted acquisition show right biliary irregularities and dilated left bile ducts filled with several small intrahepatic stones (*white arrow* in **b**). Two years later, T1-weighted transverse acquisitions with fat saturation after gadolinium chelate injection obtained at portal phase (**c**) and transverse T2-weighted acquisition (**d**) show an intrahepatic large mass with irregular contrast enhancement (*white star*). Liver biopsy confirmed the diagnosis of intrahepatic cholangiocarcioma

Conclusion

LPAC syndrome is the main hepatic condition associated with *ABCB4*/MDR3 in adults. It is mainly characterised by intrahepatic lithiasis and, in severe forms, by bile duct dilatations and rarely, secondary cholangitis.

Fig. 11 Biliary abscess formation in a 30-year-old woman. Transverse T1-weighted contrast enhanced acquisitions (**a** and **b**) show small round lesions with peripheral enhancement (*arrows*) corresponding to abscesses in segment II (**a**) and IV (**b**). The patient previously underwent right hepatectomy for multiple and diffuse bile duct stones

References

1. Deleuze JF, Jacquemin E, Dubuisson C et al (1996) Defect of multidrug-resistance 3 gene expression in a subtype of progressive familial intrahepatic cholestasis. Hepatology 23:904–908
2. Davit-Spraul A, Gonzales E, Baussan C et al (2010) The spectrum of liver diseases related to *ABCB4* gene mutations: pathophysiology and clinical aspects. Semin Liver Dis 30:134–146
3. Enjoji M, Yada R, Fujino T et al (2009) The state of cholesterol metabolism in the liver of patients with primary biliary cirrhosis: the role of MDR3 expression. Hepatol Int 3:490–496
4. Wadsworth CA, Dixon PH, Wong JH et al (2011) Genetic factors in the pathogenesis of cholangiocarcinoma. Dig Dis 201(29):93–97
5. De Vree JM, Jacquemin E, Sturm E et al (1998) Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. Proc Natl Acad Sci USA 95:282–287
6. Davit-Spraul A, Gonzales E, Baussan C et al (2009) Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis 4:1
7. Jacquemin E (2001) Role of multidrug resistance 3 deficiency in pediatric and adult liver disease: one gene for three diseases. Semin Liver Dis 21:551–562
8. Kubitz R, Bode J, Erhardt A et al (2011) Cholestatic liver diseases from child to adult: the diversity of MDR3 disease. Z Gastroenterol 49:728–736

9. Tougeron D, Fotsing G, Barbu V, Beauchant M (2012) *ABCB4/MDR3* gene mutations and cholangiocarcinomas. J Hepatol 57:467–468

10. Shoda J, Oda K, Suzuki H et al (2001) Etiologic significance of defects in cholesterol, phospholipid, and bile acid metabolism in the liver of patients with intrahepatic calculi. Hepatology 33:1194–1205

11. Erlinger S (2012) Low phospholipid-associated cholestasis and cholelithiasis. Clin Res Hepatol Gastroenterol 36:S36–S40

12. Rosmorduc O, Hermelin B, Boelle PY et al (2003) *ABCB4* gene mutation-associated cholelithiasis in adults. Gastroenterology 125:452–459

13. Ziol M, Barbu V, Rosmorduc O (2008) *ABCB4* heterozygous gene mutations associated with fibrosing cholestatic liver disease in adults. Gastroenterology 35:131–141

14. Poupon R, Arrivé L, Rosmorduc O (2010) The cholangiographic features of severe forms of *ABCB4/MDR3* deficiency-associated cholangiopathy in adults. Gastroenterol Clin Biol 34:380–387

15. Marschall HU, Einarsson C (2007) Gallstone disease. J Intern Med 261:529–542

16. Kim IS, Myung SJ, Lee SS et al (2003) Classification and nomenclature of gallstones revisited. Yonsei Med J 44:561–570

17. Van Erpecum KJ (2011) Pathogenesis of cholesterol and pigment gallstones: an update. Clin Res Hepatol Gastroenterol 35:281–287

18. Vítek L, Carey MC (2012) New pathophysiological concepts underlying pathogenesis of pigment gallstones. Clin Res Hepatol Gastroenterol 36:122–129

19. Vullierme MP, Vilgrain V (2006) Isolated or multifocal segmental intrahepatic bile duct dilatation: management. J Radiol 87:500–512

20. Vuillerme MP, Vilgrain V, Zins M et al (1997) Ultrasonographic anomalies of intrahepatic biliary ducts: contribution of the comet-tail image. Gastroenterol Clin Biol 21:103–108

21. Sugiyama M, Atomi Y, Takahara T et al (2001) Magnetic resonance cholangiopancreatography for diagnosing hepatolithiasis. Hepatogastroenterology 48:1097–1101

22. Hekimoglu K, Ustundag Y, Dusak A et al (2008) MRCP vs ERCP in the evaluation of biliary pathologies: review of current literature. J Dig Dis 9:162–169

23. Kim TK, Kim BS, Kim JH et al (2002) Diagnosis in intrahepatic stones: superiority of MR cholangiopancreatography over endoscopic retrograde cholangiopancreatography. AJR Am J Roentgenol 179:429–434

24. Safar F, Kamura T, Okamoto K et al (2005) Magnetic resonance T1 gradient-echo imaging in hepatolithiasis. Abdom Imaging 30:297–302

25. Vachha B, Sun MR, Siewert B et al (2011) Cystic lesion of the liver. AJR Am J Roentgenol 196:W355–W366

26. Mauad TH, van Nieuwkerk CM, Dingemans KP et al (1994) Mice with homozygous disruption of the mdr2 P-glycoprotein gene. A novel animal model for studies of nonsuppurative inflammatory cholangitis and hepatocarcinogenesis. Am J Pathol 145:1237–1245

27. Fickert P, Fuchsbichler A, Wagner M et al (2004) Regurgitation of bile acids from leaky bile ducts causes sclerosing cholangitis in MDR2 (*Abcb4*) knockout mice. Gastroenterology 127:261–274

28. Pauli-Magnus C, Meier PJ (2006) Hepatobiliary transporters and drug-induced cholestasis. Hepatology 44:778–787

29. Azizi L, Raynal M, Cazejust J et al (2012) MR imaging of sclerosing cholangitis. Clin Res Hepatol Gastroenterol 36:130–138

30. Wendum D, Barbu V, Rosmorduc O et al (2012) Aspects of liver pathology in adult patients with MDR3/ABCB4 gene mutations. Virschows Arch 460:291–298

31. ShaibY E-SHB (2004) The epidemiology of cholangiocarcinoma. Semin Liver Dis 24:115–125

32. Han JK, Choi BI, Kim AY et al (2002) Cholangiocarcinoma: pictorial essay of CT and cholangiographic findings. Radiographics 22:173–187