LPAC syndrome (low phospholipid-associated cholelithiasis) : Spectrum of Imaging features

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Learning objectives

The purpose of this exhibit is to review:

- the LPAC syndrome definition
- the association of LPAC syndrome with MDR3/ABCB4 gene mutation
- the spectrum of imaging features in this pathology

Background

Definition:

The LPAC syndrome is a rare genetic disorder, characterized by three most important elements: biliary symptoms before the age of 40, recurrence of the symptoms after cholecystectomy and intrahepatic microlithiasis or intrahepatic hyperechogenic foci.

Other minor criteria have been described, such as mild chronic cholestasis, at least one episode of cholangitis, acute pancreatitis or biliary colic, efficiency of ursodesoxycolic acid (UDCA) and similar symptoms in first degree relative.

ABCB4 gene mutations have been described in patients with LPAC syndrome in 25 to 56% of cases.

Physiopathology:

ABCB4 gene encodes for MDR3 (multidrug resistance 3P glycoprotein). MDR3 are phospholipid translocators involved in biliary phosphatidylcholine excretion. The result of these mutations is a lack of phosphatidylcholine in bile.

- Phosphatidylcholine normally chaperones bila acids, preventing damage to the biliary epithelium. The "unchaperoned" bile acids in bile of patients with MDR3 deficiency cause a chronic cholangitis.
- Phosphatidylcholine normally also transports biliary cholesterol. Patients with MDR3 deficiency have increased cholesterol saturation in bile, resulting in cholesterol precipitation and gallstone formation.

**Imaging findings OR Procedure details**

Imaging features associated with ABCB4/MDR3 mutations are not specific and correspond to a wide spectrum of biliary abnormalities.

The main findings is the presence of **intrahepatic lithiasis**: US examination is very accurate in detecting intrahepatic stones: they appear as heterogeneous and echoic foci centered on the intrahepatic ducts, or as "comet-tail artifact" due to US reverberation (figure 1).

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 equivalent to ERCP in choledocholithiasis diagnosis and superior to ERCP in intrahepatic lithiasis diagnosis.

Magnetic Resonance Cholangiopancreatography (MRCP) shows the presence of round or oval shape signal voids in the lumen of the bile ducts on heavily T2-weighted sequences (figures 8,9). Stones may have high signal on T1-weighted sequences (figure 7) or strong hypointensities on T1-weighted acquisitions (figure 11). The stones appear as endoluminal signal voids on T2-weighted acquisition (figures 6, 10).

A complementary exploration by US and MRI should be recommended because MR is not able to detect very small stones, while US may be difficult in case of massive intraluminal stones (figure 2).

Atypic features are:

- **Bile ducts dilatations**:

  When bile duct dilatations are present, they appear as mild to moderate. Rarely, patients may present with more severe dilatations (<10%). Such severe bile duct dilatation
may only involve one or two liver segments (figures 3,4,5) or may be diffuse. 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 embryologic 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 and the aggression of the bile epithelium and consist in uni or multifocal noncystic large spindle-shaped bile duct dilatations that can concern one to several hepatic segments, associated with regular non-dilated ducts. 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. 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.

- **Sclerosing cholangitis** (figure 12, 13)

In mice, the multidrug resistance (MDR) glycoproteins that mediate the translocation of phosphatidylcholine across the canalicular membrane of the hepatocyte, and corresponding to MDR3 in man, is called MDR2. Whereas the main feature in mdr2 knock-out mice, which corresponds to the equivalent animal model of human MDR3 deficiency, 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. 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 etiologies in which several genes such as *ABCB4/MDR3* may play a disease modifier role. To support this conceptual view, our group recently reported for the first time, in a series of 13 patients with MDR3 deficiency, imaging presentations mimicking sclerosing cholangitis in 2 patients at MR (Figure 12). They corresponded to small duct fibro-obliterative lesions at pathology, and may be due to the direct toxic effect of biliary acids on epithelioma. 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*.

All complications associated with chronic cholangitis and/or cholelithiasis have been described in patients with LPAC syndrome: intrahepatic cholangiocarcinoma (figures 14, 15, 16, 17), portal hypertension, superinfection (figure 18), hepatic fibrosis or cirrhosis.
Intrahepatic cholangiocarcinoma is a rare primary liver tumor (10-20%). Recently, Tougeron et al. reported 2 cases of IHCC in different and unrelated families with MDR3 deficiency. In both cases, no argument supporting the direct relation between \( ABCB4 \) mutations and tumorogenesis 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.

**Images for this section:**

**Fig. 1:** Ultrasound in a 44-year-old man with LPAC syndrome Transverse ultrasound showing typical comet-tail artefacts in the left lobe.
Fig. 2: MRCP for the same patient than figure 1: US/MRCP discrepancy. The MRCP shows no sign of biliary stone.
Fig. 3: Unifocal mild biliary dilatation in a 40-year-old man with LPAC syndrome. The dilatation is located in the segment V on 3D MCRP and contains a small signal void corresponding to an endoluminal stone (white arrow). The gallbladder and the common bile duct show no abnormalities.
**Fig. 4:** Severe uni-segmental dilatation in a 44-year-old woman with LPAC syndrome. Transverse T2-weighted acquisition with fat saturation. Several dilated bile ducts in segment VIII containing a macroscopic signal void corresponding to a biliary stone (white arrows).
Fig. 5: Severe uni-segmental dilatation in a 44-year-old woman with LPAC syndrome (same than figure 4). 3D MRCP. Several dilated bile ducts in segment VIII containing a macroscopic signal void corresponding to a biliary stone (white arrows).
**Fig. 6:** Global bile duct abnormalities in a 48-year-old man with LPAC syndrome. Transverse T2-weighted acquisition shows a biliary dilatation in both right and left lobes containing biliary stones depicted as T2 hypointense endoluminal formations.
Fig. 7: Global bile duct abnormalities in a 48-year-old man with LPAC syndrome. Transverse T1-weighted acquisition with fat saturation shows a biliary dilatation in both right and left lobes containing biliary stones depicted as T1 hyperintense endoluminal formations (white arrow).
**Fig. 8:** Global bile duct abnormalities in a 48-year-old man with LPAC syndrome. Coronal maximum intensity projection MCRP shows a biliary dilatation in both right and left lobes and large round signal voids in the dilated bile ducts (white arrow) corresponding to a biliary stone.
Fig. 9: Unifocal dilatation of segment VI biliary duct filled with several stones in a 69-year-old man with LPAC syndrome. Coronal maximum intensity projection (MCRP) shows an unifocal dilatation of segment VI biliary duct filled with several stones.
**Fig. 10:** Unifocal dilatation of segment VI biliary duct filled with several stones in a 69-year-old man with LPAC syndrome. Transverse T2-weighted acquisition shows an unifocal dilatation of segment VI biliary duct filled with several stones (white arrow). The stones appear as endoluminal signal voids on T2-weighted acquisition.
**Fig. 11:** Unifocal dilatation of segment VI biliary duct filled with several stones in a 69-year-old man with LPAC syndrome. Transverse in-phase T1-weighted acquisition shows an unifocal dilatation of segment VI biliary duct filled with several stones (strong hypointensities on T1-weighted acquisitions).
**Fig. 12:** Diffuse and severe cholangitis in a 64-year-old woman Maximum intensity projection coronal MRCP shows biliary irregularities and stenosis.
**Fig. 13:** Diffuse and severe cholangitis in a 64-year-old woman T1-weighted transverse acquisitions with fat saturation after gadolinium chelate injection obtained at portal phase show biliary irregularities and stenosis associated with intense biliary contrast uptake of the thickened biliary walls. Note the segment I hypertrophy (white star).
**Fig. 14:** Severe LPAC syndrome with secondary intrahepatic cholangiocarcinoma formation in a 55-year-old woman. Maximum intensity projection coronal MRCP shows right biliary irregularities and dilated left bile ducts filled with several small intrahepatic stones.
Fig. 15: Severe LPAC syndrome with secondary intrahepatic cholangiocarcinoma formation in a 55-year-old woman Transverse T2-weighted acquisition shows right biliary irregularities and dilated left bile ducts filled with several small intrahepatic stones (white arrow).
**Fig. 16:** Severe LPAC syndrome with secondary intrahepatic cholangiocarcinoma formation in a 55-year-old woman. Two years later, T1-weighted transverse acquisitions with fat saturation after gadolinium chelate injection obtained at portal phase show an intrahepatic large polylobulated mass with irregular contrast enhancement (white star). Liver biopsy confirmed the diagnosis of intrahepatic cholangiocarcinoma.
**Fig. 17:** Severe LPAC syndrome with secondary intrahepatic cholangiocarcinoma formation in a 55-year-old woman. Two years later, transverse T2-weighted acquisition shows an intrahepatic large polylobulated mass with high signal. Liver biopsy confirmed the diagnosis of intrahepatic cholangiocarcinoma.
Fig. 18: Biliary abscess formation in a 30-year-old woman. Transverse T1-weighted contrast enhanced acquisitions (A and B) show small round lesions with strong peripheral rim enhancement without bile duct dilatation (arrows) without bile duct dilatation corresponding to abscesses in segment II (A) and IV (B). The patient previously underwent right hepatectomy for multiple and diffuse bile duct empierrrement stones.
Conclusion

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

References