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REVIEW

Low-Phospholipid Associated Cholelithiasis (LPAC) syndrome: A synthetic review

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Intrahepatic lithiasis;
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Summary Low-Phospholipid Associated Cholelithiasis (LPAC) is a genetic disease responsible for the development of intrahepatic lithiasis. It is associated with a mutation of the ABCB4 gene which codes for protein MDR3, a biliary carrier. As a nosological entity, it is defined by presence of two of the three following criteria: age less than 40 years at onset of biliary symptoms, recurrence of biliary symptoms after cholecystectomy, and intrahepatic hyperechogenic foci detected by ultrasound. While the majority of clinical forms are simple, there also exist complicated forms, involving extended intrahepatic lithiasis and its consequences: lithiasis migration, acute cholangitis, intrahepatic abscess. Chronic evolution can lead to secondary sclerosing cholangitis or secondary biliary cirrhosis. In unusual cases, degeneration into cholangiocarcinoma may occur. Treatment is built around ursodeoxycholic acid, which yields dissolution of biliary calculi. Complicated forms may call for interventional, radiological, endoscopic or surgical treatment. This synthetic review illustrates and summarizes the different aspects of this entity, from simple gallbladder lithiasis to cholangiocarcinoma, as well as secondary biliary cirrhosis requiring liver transplant, on the basis of clinical cases and the iconography of patients treated in our ward.

Introduction

While the incidence of vesicular cholesterol cholelithiasis in the general population is elevated, only 10 to 25% of patients are symptomatic. In cases of familial, early or diffuse intrahepatic cholelithiasis (gallstones), genetic origin should be suspected. In 2001, Rosmorduc et al. described

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for the first time a connection between a mutation of gene MDR3 and ''intrahepatic and gallbladder cholesterol-cholelithiasis'' [1]. Over the following years, this clinical entity was documented in association with the pathophysiological process now known as ''Low-Phospholipid Associated Cholelithiasis (LPAC) Syndrome'' [2,3]. Initially considered as responsible for less than 5% of symptomatic cholelithiasis cases [2,4], incidence of the LPAC syndrome may in fact be more frequent, affecting up to 25% of women under 30 years of age with symptomatic cholelithiasis [5]. Improved understanding of this recently described nosological entity and widespread divulgation of its diagnostic criteria should facilitate the screening and treatment of patients.

Pathophysiology

Bile is composed of a mixture of cholesterol, bile acids, phospholipids (including phosphatidylcholine) and waste (including bilirubin). Balance between these constituents ensures the stability of bile and hepatobiliary functioning.

A mutation of the ABCB4 gene (ATP-Binding Cassette, subfamily B, member 4), which is responsible for dysfunction of protein MDR3 (MultiDrug Resistance 3), causes reduced biliary phosphatidylcholine concentration. This phospholipid is a carrier and solvent of cholesterol via the formation of mixed micelles in association with bile acids. Phosphatidylcholine deficiency transforms the mixed micelles into simple micelles, which solubilize less cholesterol, meaning that cholesterol gallstones are precipitated into the bile ducts. Phosphatidylcholine also fulfills a protective function with regard to the biliary epithelium by limiting the detergent effect of bile salts. MDR3 deficiency leads to chronic attack of the biliary epithelium, an inflammatory reaction responsible for increased GGT (gamma glutamyl transpeptidase) and the precipitation of cholesterol in the different bile ducts (intrahepatic lithiasis) [1,4].

This pathophysiological process is schematized and summarized in Fig. 1.

Genetics

The LPAC syndrome is associated with mutation of the ABCB4 gene located on chromosome 7, locus 21 (7q21), which codes for protein MDR3 [1,3]. Protein MDR3 functions as a carrier of phosphatidylcholine from the lumen of the hepatocyte to the lumen of the biliary canaliculi at the level of the biliary pole of the hepatocyte. Genetic polymorphism is of prime importance, and numerous mutations have been reported: nonsense mutation, missense mutation, partial gene deletion, etc. [3,4,6–9]. One or more mutations of the gene have been detected in 50 to 65% of the patients suffering from LPAC syndrome [3,4,6,10]. As regards patients without this mutation, several explanations have been put forward:

- mutation in the unexplored regions of a gene (introns);
- mutation on a gene promoter;
- mutation in a regulatory region;
- mutation of another gene or another biliary carrier (ABCB11 or BSEP, ABCC2, ABCG5/ABCG8, etc.);
- synonymous mutation influencing production or regulation of the gene, etc. [3,4,6,11].

A majority of mutations are heterozygous missense mutations and involve ATP-Binding transmembrane parts of the protein [3,6].

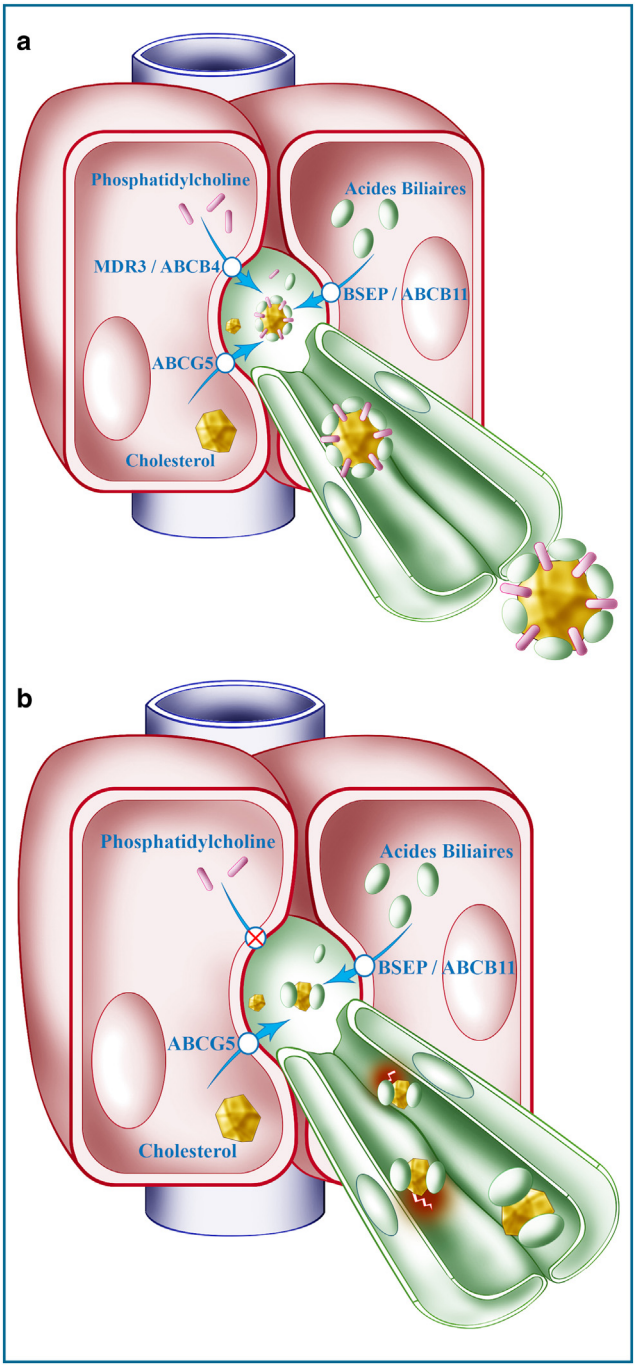

Figure 1. Pathophysiology of the LPAC syndrome; a: normal physiology: phosphatidylcholine is excreted by the MDR3 protein in the bile canaliculi at the level of the biliary hepatocyte pole. The micelles having been formed are mixed and stable, and cholesterol is solubilized in the bile; b: LPAC syndrome: The MDR3 protein (MultiDrug Resistance 3) is absent or deficient. In the absence of phosphatidylcholine, the micelles become simple, unstable and less able to solubilize cholesterol. The cholesterol precipitates and forms calculi. Along with lack of the protective effect of phosphatidylcholine, the presence of micro-crystals leads to chronic attacks on the cholangiocytes. The hepatocytes are designated in red, and the cholangiocytes in green. In the foreground in blue, a central lobular venule appears.

In cases of LPAC syndrome, search for a genetic mutation must be systematic. Indeed, even though diagnosis is based on clinical and radiological criteria, genetic research allows for genetic counseling in the event of a mutation. Moreover, systematic search for genetic mutation of the ABCB4

gene should facilitate detection of new mechanisms responsible for the syndrome and render genetic screening more effective [3,5,6,12].

The nosological spectrum of the ABCB4 gene is quite wide: LPAC syndrome, Progressive Familial Intrahepatic Cholestasis Type 3 (PFIC3), gestational cholestasis, drug or contraceptive-induced cholestasis, unexplained cholestasis, etc. [8].

According to different studies, a mutation of the MDR3 gene has been identified in 7 to 77% of patients suffering from gestational cholestasis [13]. In 2010 Poupon et al. reported a mixed clinical case in which the distinction between LPAC syndrome and PFIC3 was far from obvious. In synthesis, PFIC3 patients seldom develop lithiasis, while LPAC patients seldom develop extensive fibrosis [7].

In cases of homozygous nonsense mutation, patients develop a serious form of the childhood disease PFIC3 at an earlier stage of life; this illness associates neonatal cholestasis, biliary cirrhosis during adolescence and hepatic failure prior to adulthood. The affected patients show no residual MDR3 activity [1,14,15]. A theory of minimum level of activity has been drawn up to explain the strikingly high variability between genotype and phenotype:

- each mutation is likely to have a different impact on residual MDR3 activity;
- presence of a heterozygous, composite heterozygous or homozygous mutation likewise has an influence;
- lastly, while an influence of environmental factors on level of activity is difficult to indicate with precision, it surely comes into play.

Epidemiology

Prevalence of the LPAC syndrome is unknown but considered as quite low [3]. According to the LPANGH cohort (LPAC cohort of the *Association Nationale des Hépato-Gastroentérologues des Hôpitaux Généraux de France*), it is present in approximately 1% of symptomatic cholelithiasis patients [16]. It mainly affects women, with a sex ratio close to 3/1 [3,6,16]. Average age at symptom onset is 29.1 years for women and 38.7 years for men; onset occurs earlier in the event of nonsense, homozygous or composite heterozygous mutation [6]. The LPAC syndrome is primarily a disease of young adulthood; it is seldom observed in adolescents and only exceptionally in children. Sexual and consequently hormonal immaturity probably protects the youngest patients from syndrome occurrence [17]. Contrary to classical gallstone disease, the LPAC syndrome occurs in patients of low or normal weight. In fact, only 3% of LPAC syndrome patents display body mass index superior to 25 kg/m^2 [12].

Diagnostic criteria

The LPAC syndrome is defined by the existence of two of the three following criteria: (1) age at onset of less than 40 years, (2) recurrence of symptoms after cholecystectomy and (3) presence of hyperechogenic intrahepatic foci detected by ultrasound, sludge or intrahepatic microlithiasis [2—4].

A number of minor diagnostic criteria also come into play: family history of biliary lithiasis among first-degree relatives, past history of gestational cholestasis, sensitivity to ursodeoxycholic acid treatment [2,3].

Dong et al. recently reported a pronounced association between LPAC syndrome and lithiasis of the common bile duct in young non-cholecystectomized patients [16].

Diagnosis of LPAC syndrome is based on the above-mentioned diagnostic criteria, on radiological aspects, on analysis of the composition of the bile collected during catheterization and on search for a mutation of the ABCB4 gene [3,5,6,12]. Analysis of bile is not recommended in routine clinical examination. While a mutation of the ABCB4 gene is present in only 56 to 65% of cases, its absence does not invalidate LPAC syndrome diagnosis.

Family screening is recommended when the index case shows a proven mutation, the objective being to offer tailored family-centered genetic counseling [3,5,6,12].

Clinical aspects

Biliary lithiasis (gallstone) is symptomatic in LPAC syndrome, with typical biliary pain leading to cholecystectomy in over 90% of cases [3]. Recurrent symptoms following cholecystectomy are a cause for concern, given their association with intrahepatic lithiasis or lithiasis migration. In rare cases, a patient may be suffering from acute cholecystitis, acute cholangitis or acute pancreatitis [1—3]. Serious complications (pancreatitis, acute cholangitis, intrahepatic lithiasis) seem to be more frequent in men [6]. Their recurrence subsequent to cholecystectomy suggests their being more closely associated with intrahepatic than with vesicular lithiasis.

Gallbladder lithiasis is invariably present in LPAC syndrome. Frequently associated, intrahepatic lithiasis is massive in 5 to 10% of cases [7]. It may be unifocal or multifocal, and is responsible for fusiform dilatation of the bile ducts with gallstone obstruction but without downstream stenosis.

The biliary calculi present in LPAC syndrome are yellow and saturated with cholesterol. Analysis of bile reveals an elevated cholesterol/phospholipid ratio [1,3]. It can be associated with biological cholestasis, particularly as regards GGT levels, and is likely to be connected with chronic cholangiocyte aggression [1,3].

In 50% of their pregnancies, LPAC syndrome patients develop gestational cholestasis [6]. Women's sensitivity to this syndrome is related to secretions of hormones (estrogens...) that favor its occurrence. These secretions explain the pronounced association between LPAC syndrome and gestational cholestasis, cholestasis induced by oral contraception, and frequent onset of the initial symptoms following pregnancy. Some medications can also favor the appearance of LPAC, due to interference with the biliary carriers, modified regulation of biliary carrier expression, or toxic cholangiopathy.

The main diagnostic elements differentiating classical gallbladder lithiasis from lithiasis in the LPAC framework are summarized in Table 1.

The main differential diagnoses correspond to two large-scale etiological categories: (1) pain following cholecystectomy without intrahepatic lithiasis and (2) residual intrahepatic lithiasis. Pain after gall bladder removal may be due to Sphincter of Oddi dysfunction, to residual lithiasis of the common bile duct or to complications subsequent to sphincterotomy. Verification of the vacuity of the common bile duct and examination of the patient's clinical history allow for rapid elimination of these situations. In the event of painful intrahepatic lithiasis following cholecystectomy,

Table 1 Elements of diagnostic orientation differentiating classical gallbladder lithiasis from lithiasis in the context of LPAC syndrome.

	Classical gallbladder lithiasis	Lithiasis in the context of LPAC syndrome
Age at onset of first symptoms	After 50 years	Before 30 years
Morphotype	Association with excess weight, obesity	Normal weight
Sex	Sex ratio 1.5 women/1 men	Sex ratio 3 women/1 man
Imagery	Isolated gallbladder lithiasis	Associated intrahepatic lithiasis
Family history	—	1st-degree familial lithiasis, symptomatic before 40 years
Personal history	—	Gestational cholestasis
Cholecystitis	Frequent	Rare
Lithiasis complications	Rare	Frequent (migration, acute cholangitis, acute pancreatitis, etc.)
Recurrence of symptoms after cholecystectomy	Rare	Very frequent (by definition)

the nosological framework of intrahepatic lithiasis becomes relevant. One possible diagnosis is bilirubinoid lithiasis (following hematological disease), of which the clinical history is evident enough. Other possible diagnoses include pathological choledocholithiasis: congenital abnormalities (Caroli disease...), primary sclerosing cholangitis (PSC) or, more rarely, post-traumatic stenoses. Given their clinical histories and radiological characteristics, these pathologies are easily distinguishable from LPAC syndrome [3,4]. For example, PSC is commonly associated with inflammatory bowel disease or the presence of auto-antibodies. While Rosmorduc et al. made no connection between mutation of the ABCB4 gene and PSC occurrence [3,18], other authors have reported several cases of association [19,20]. An additional nosological framework involves intrahepatic lithiasis with normal bile ducts: LPAC syndrome is essentially implicated.

Radiology

Radiological examinations are of central importance in positive diagnosis of LPAC syndrome. They need to be carried out and interpreted by a radiologist having been informed about the diagnostic suspicion. The detection rate of signs of LPAC syndrome can range from 5% (non-initiated radiologist) to 90% (expert radiologist) (LPANGH study) [5].

Ultrasonography is performed in first intention and can detect ''telltale'' signs in 80 to 85% of the patients [4]:intrahepatic hyperechoic foci with posterior acoustic shadowing or ''comet tail'' images disseminated along the portal axis, intrahepatic sludge, micro-lithiasis [1—4,21] (Fig. 2). Doppler ultrasound highlights the color comet-tail artifacts known as ''twinkling artifacts'', which are signs of microlithiasis; contrary to pneumobilia, they are not mobile [4]. When intrahepatic stones are numerous, their appearance is concomitant with dilation of not only the proximal, but also the peripheral intrahepatic bile ducts, a phenomenon suggesting intrahepatic lithiasis.

While CT scan and magnetic resonance imaging (MRI) likewise reveal these different dilations and stones, they may be limited with regard to micro-lithiasis [3,21,22]. Non-cystic, spindle-shaped unifocal or multifocal bile duct dilatations are associated with intrahepatic lithiasis and alteration of the biliary epithelium [21,22] (Fig. 3). Contrary to Caroli disease, they manifest no association with ductal plate malformation and consequently no central dot sign [22], as biliary tract dilatation invariably remains secondary to the development of lithiasic disease.

Cross-sectional imaging can detect a number of complications: chronic cholangitis (Fig. 4), acute cholangitis (Fig. 5), intrahepatic abscess (Fig. 5), hepatic dysmorphia (atrophy of maximally damaged areas), signs of portal hypertension and, very rarely; intrahepatic cholangiocarcinoma (bile duct cancer) [22].

Endoscopic ultrasound is indicated only when intervention is considered since MRI is a non-invasive examination providing equivalent results [22].

Carried out during a radiological or endoscopic interventional procedure, cholangiography is liable to reveal intrabiliary abnormalities: dilatation, calculi, stenoses, etc. (Fig. 6).

Pathologic examination

Histological analysis is unspecific and variable. Macroscopic examination permits observation of intrahepatic lithiasic disease, which may be associated with biliary tract thickening suggestive of angiocholitis (Fig. 7a).

From a histological standpoint, no pathognomonic lesion appears; on the other hand, discrete, isolated or associated signs point to biliary duct obstruction. These signs include: portal enlargement, occasional early-stage septal fibrosis, ductular proliferation, mononuclear or polymorphous discrete chronic portitis, and discrete capillary cholestasis (Fig. 7b). Wendum et al. have reported rare cases of

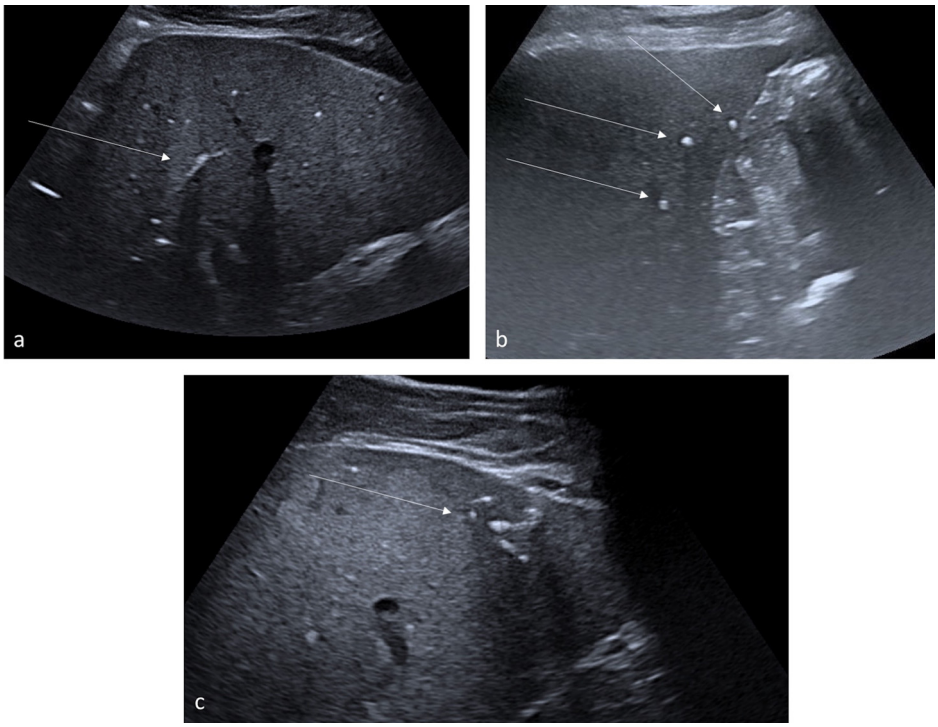

Figure 2. B-mode ultrasound imaging; a: Comet-tail image with posterior acoustic shadowing in the right lobe (arrow); b: hyperechoic intrahepatic calculi in the left lobe (arrows); c: peripheral lithiasis of the left lobe, hyperechoic, relatively extended (arrow). Different patients appear on each vignette.

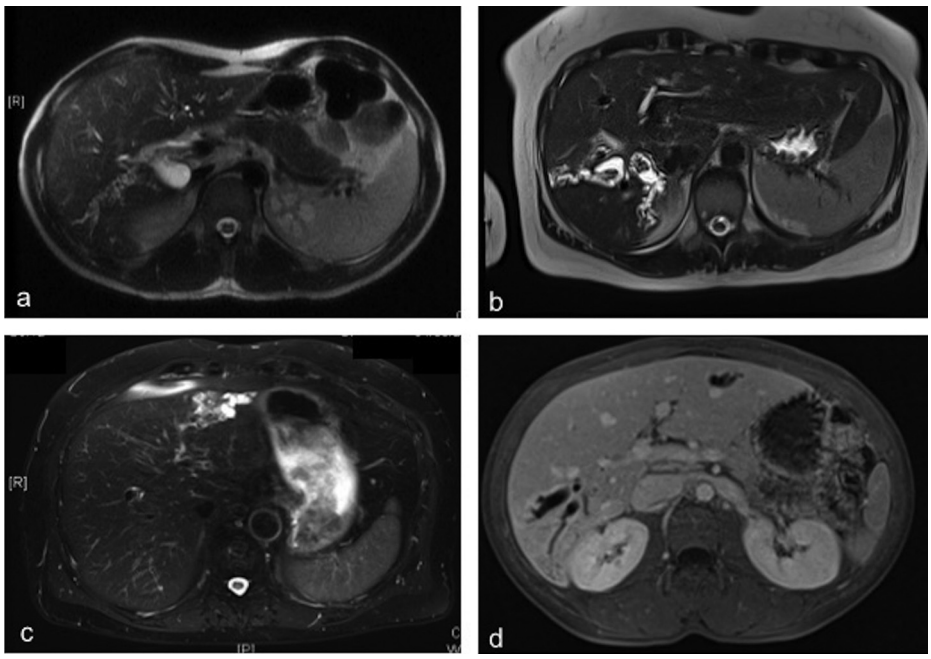

Figure 3. Intrahepatic lithiasis in MRI; a: T2 Haste sequence: posterolateral sectoral microlithiasis. A 20-year-old male patient. Satisfactory evolution with ursodeoxycholic acid; b: T2 Haste sequence: posterolateral sectoral lithiasis with macro-lithiasis and biliary tract dilatation; a 43-year-old female patient. Refusal of hepatectomy and evolution to cholangiocarcinoma; c: T2 Haste sequence: lithiasis of segment III with atrophy of this segment. A 56-year-old male patient. Partial effectiveness of ursodeoxycholic acid. Left lobectomy; d: sequence T1 Fat Sat with injection of gadolinium during portal phase: lithiasis of the right posterolateral sector and segment III. A 41-year-old female patient. Partial effectiveness of ursodeoxycholic acid. Right posterolateral sectoriectomy.

''onion bulb'' pericanalary fibrosis or fibrous canal scarring [23] that may suggest primary sclerosing cholangitis of the small canals. However, the context was that of lithiasic disease, without associated colonic inflammation. ultimately, cholesterol microcrystals should alert the pathologist; these lanceolate formations are optically empty (Fig. 7c).

Evolutive complications may be revelatory and should be sought out, particularly dysplasia of the biliary epithelium and/or cholangiocarcinoma [23] (Fig. 7d). To achieve satisfactory highlighting, numerous surgical specimen collections are necessary. Extrinsic to the context of lithiasic disease, cryptogenic cirrhosis can be a presentation mode [8,23,24].

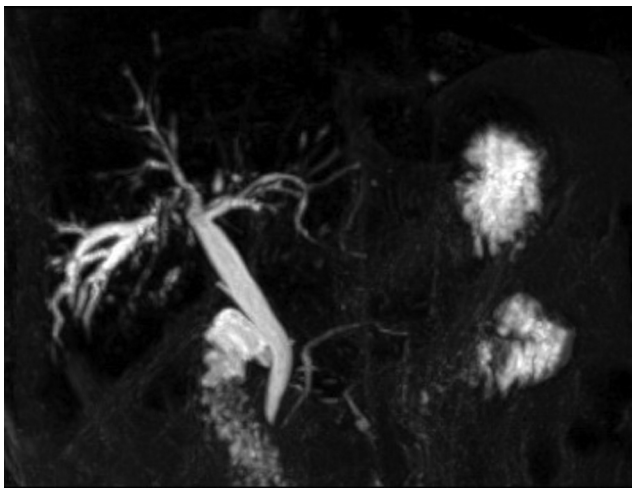

Figure 4. MIP reconstruction of a 3D bili-MR sequence. Visualization of the cholangitic aspect of the biliary tree, with dilatations and segmental stenoses. The right ducts are dilated and the left ducts are the site of diffuse stenoses. A 44-year-old female patient having experienced adverse evolution notwithstanding medical treatment, and whose condition necessitated liver transplant (Fig. 6).

When carried out in a normal subject, immunohistochemical analysis of the antibody MDR3 reveals capillary hepatocyte banding. While this type of immunoreactivity may be normal in the discreet forms of LPAC syndrome, its presence not exclude the diagnostic. When it diminishes or disappears, the diagnostic is confirmed [20,23].

Clinical forms—Risks of evolution

The typical clinical form is represented by recurrent typical biliary pain following cholecystectomy, in a patient less than 30 years of age at symptom onset [4].

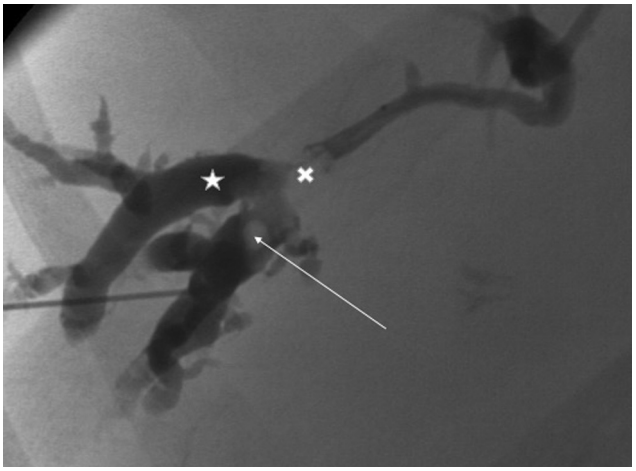

Figure 6. Cholangiography during radiological biliary drainage by percutaneous approach. Visualization of dilatation of the bile ducts (star), of endobiliary calculi (arrow) and of a biliary stenosis (cross). A 44-year-old female patient with LPAC syndrome confirmed by genetic analysis and resistant to medical treatment. Her history has begun with cholecystectomy at the age of 15 years, followed by two episodes of gestational cholestasis at 23 and 27 years of age, and multiple endoscopic treatments since the age of 35. Due to massive liver damage, she was transplanted at the age of 46, with a satisfactory outcome at 6 years after liver transplantation. Hers is a familial form; her daughter also suffers from LPAC syndrome.

Evolution with optimal medical treatment by ursodeoxycholic acid (UDCA) is quite satisfactory; in a majority of cases the symptoms disappear, and when treatment is pursued, recurrence is rare [3,6] (Fig. 8). However, one third of the patients presenting complications require a number of endoscopic operations (or liver resection), and maternal-fetal complications may occur in cases of gestational cholestasis [6].

More often than not, intrahepatic lithiasis is microscopic, but in 5 to 10% of cases, lithiasis is macroscopic, sectoral,

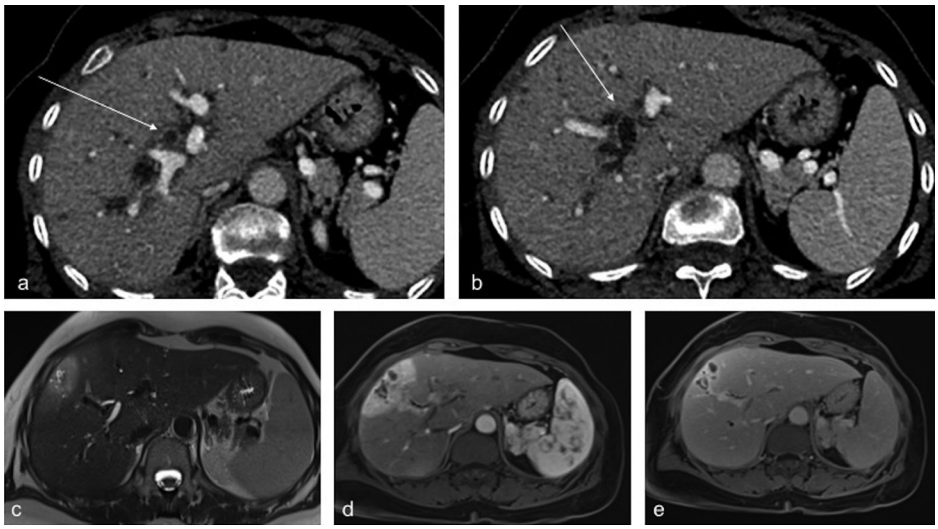

Figure 5. Intrahepatic complications of LPAC syndrome; a and b: CT with injection during portal phase: parietal contrast enhancement of the dilated biliary convergence and right canal (arrows) revealing cholangitis; c: bili-MRI: dilatation of the small peripheral bile ducts, with (on contact) a hepatic zone on T2 hypersignal, displaying parenchymatous edema; d: MRI, T1 sequence with gadolinium injection (arterial phase): these lesions are related with parenchymatous perfusion disorders and abscesses being formed; e: MRI, T1 sequence with gadolinium injection (portal phase): dilated peripheral bile ducts and pronounced enhancement of the abscess walls. A 63-year-old patient cholecystectomized at the age of 22 years and having repeatedly reported choledochal and right biliary tract stones, responsible for recurrent angiocholitis and intrahepatic abscess formation. Treatment with ursodeoxycholic acid was partially effective, leading to hepatectomy to treat infectious complications.

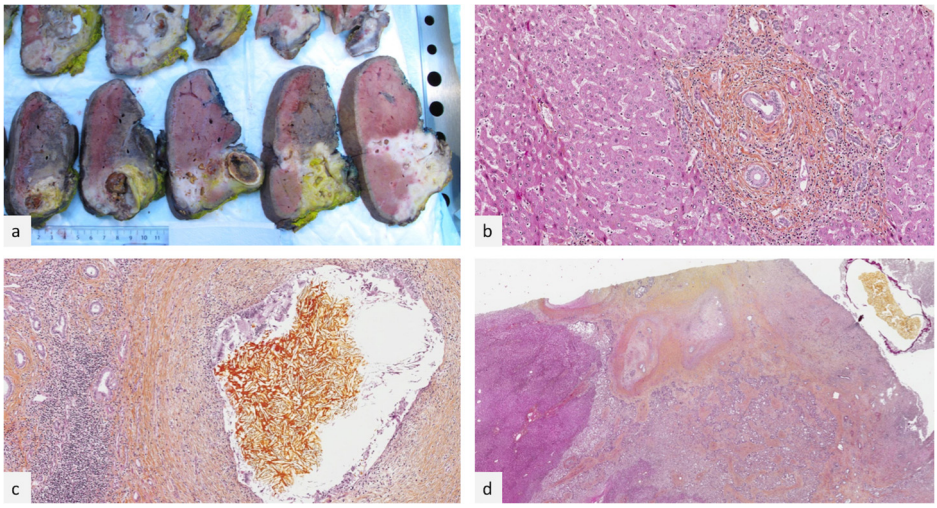

Figure 7. Microscopic and macroscopic views; a: Macroscopic view of hepatectomy specimen: intrahepatic lithiasis with inflammatory dilatation of the bile ducts; b: portal fibrosis with ductular proliferation leading to diagnosis of biliary obstruction; c: lanceolate cholesterol crystals viewed in the light of a septal biliary canal; d: peri-hilar cholangiocarcinoma.

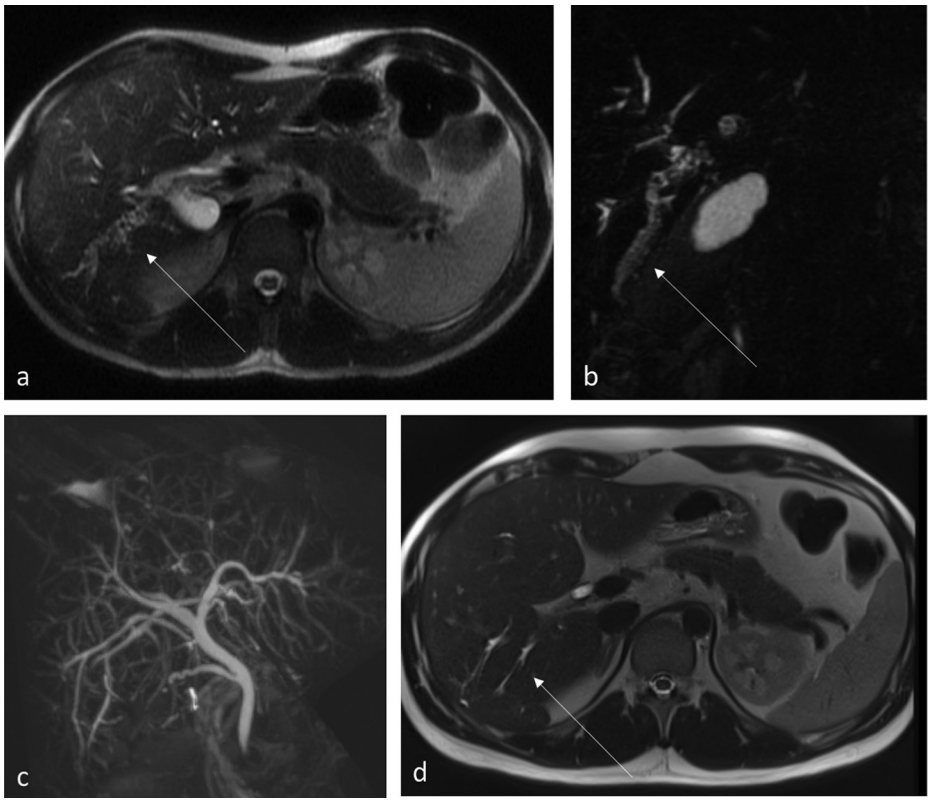

Figure 8. Remarkable evolution with ursodeoxycholic acid; a: MRI in T2 Haste sequence, axial section: stones in the posterolateral sector (arrow); b: MRI 3D-Bili sequence, coronal reconstruction: stones in the posterolateral sector (arrow); c: coronal reconstruction MIP Bili-RM 3D following six months of treatment with ursodeoxycholic acid: complete disappearance of biliary tract stones in the posterolateral sector; d: MRI in T2 Haste sequence, axial section: disappearance of the stones in the posterolateral sector (arrow). Patient cholecystectomized at the age of 20. Recurrent angiocholitis episodes led to discovery of biliary tract stones in the posterolateral sector, which were treated ineffectively by several sphincterotomies and biliary endoprostheses. Highlighting of an ABCB4/MDR3 mutation at the age of 22 prompted initiation of an ursodeoxycholic acid treatment that was remarkably effective, with symptom improvement in a few weeks and normalized imagery in 6 months.

and unifocal or multifocal and it is responsible for repeated angiocholitis, pain and hepatic abscesses [7]. While intrahepatic calculi may justify exclusively medical treatment, hepatic resection surgery is far from exceptional, especially since the syndrome is often unrecognized when caregiving starts.

Chronic infections and chronic aggression of the bile ducts by lithiasis and hydrophobic bile acids can be responsible for subsequent evolution leading to secondary biliary cirrhosis [3,6,19,20] or secondary sclerosing cholangitis [22,23] (Fig. 4). From the cirrhosis, hepatocellular carcinoma lesions are liable to develop [23]. An association

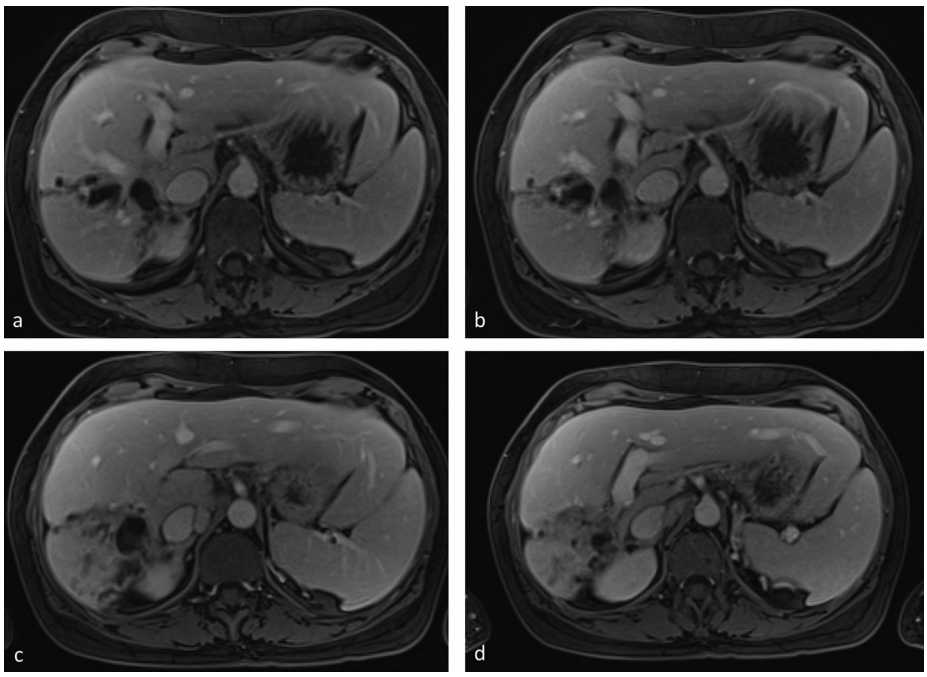

Figure 9. Hepatic MRI—T1 Fat-Sat sequence with gadolinium injection in portal phase. Evolution toward cholangiocarcinoma. In 2014 MRI (vignettes a and b), biliary tract dilatation in the posterolateral sector (above the calculi in the bili-MRI sequences, Fig. 3). In 2017 (vignettes c and d), dilatation increased due to heightening tissue infiltration. Biopsies confirmed cholangiocarcinoma. Female patient monitored since the age of 37 years for intrahepatic lithiasis. Given her symptoms, right hepatectomy was proposed when the patient was 43, but she repeatedly refused to be operated. Four years later, a new angiocholitis episode revealed histologically proven cholangiocarcinoma. Right hepatectomy extended to the vena cava and biliodigestive anastomosis allowed a RO resection, but peritoneal carcinomatosis occurred one year later.

between intrahepatic lithiasis and risk of cholangiocarcinoma has been reported and is now recognized, particularly in Asian series. In the presence of LPAC syndrome, on the other hand, the cases of cholangiocarcinoma described in the literature are few [4,6,10,23,25] (Fig. 9). Its pathophysiology, which has yet to be satisfactorily elucidated, is apparently related to chronic aggression of the biliary epithelium by calculi and hydrophobic bile acids, which may cause chronic inflammation and ensuing dysplasia. While a genetic predisposition having to do with a mutation of the ABCB4 gene is not to be excluded, it seems highly unlikely.

All in all, throughout the literature and in our own clinical experience, the risk of evolution leading to cirrhosis or malignant transformation is undeniable [3,4,6,10,19,20,22,23,25]. The incidence of this complication is still unknown but certainly rare.

Treatment

Medical treatment

Treatment of LPAC syndrome patients is built around ursodeoxycholic acid (UDCA). Ursodeoxycholic acid is a hydrophilic biliary acid. Its mechanisms of action are multiple:

- it potentiates the effect of MDR3 by increasing its residual activity through mechanisms of regulation and intracellular signaling;
- it protects the biliary epithelium by decreasing the detergent effect of the hydrophobic bile acids;
- it reduces the quantity of hydrophobic bile acids while increasing the pool of hydrophilic bile acids by means of intracellular signaling mechanisms (synthesis, import, export, hydroxylation, sulfation and conjugation of bile acids) and reduced intestinal reabsorption of endogenous bile acids;
- it solubilizes cholesterol;
- it decreases inflammation by reducing the expression of pro-inflammatory cytokines;
- it increases bile secretion, particularly that of its alkaline compounds [1,3,4,26,27].

Recommended daily dosage ranges from 7 to 10 mg/kg/d, but it can be heightened to 20 mg/kg/d [1,4,6]. It is not necessary to wait for genetic confirmation of the diagnosis before initiating UDCA treatment.

A majority of patients are effectively treated by UDCA. It has a rapid positive impact on symptomatology and biological tests. And while its effect on imaging examinations is often delayed, it can at times be spectacular (Fig. 8). The hypothesis put forward is that the symptomatology and damage to the biliary epithelium are probably due to cholesterol micro-crystals rather than large calculi [1].

Dietary regimens are ineffective and not recommended. In cases of hypercholesterolemia, statin treatment is preferable to fibrate treatment [3,4]. And when LPAC syndrome appears following the initiation of estrogen-progestin treatment, the need for the latter will need to be assessed, and alternatives will be explored.

Surgical and interventional treatment

A majority of LPAC syndrome patients have been cholecystectomized prior to diagnosis of the syndrome. If this is not the case, cholecystectomy should not be systematically carried out; that much said, it is to be recommended in the event of symptomatic vesicular lithiasis. One common stumbling block consists in determining whether the

symptomatology should be ascribed to gallbladder lithiasis or intrahepatic damage [3,4]. Only in cases of acute cholecystitis is cholecystectomy clearly indicated. In other cases (acute pancreatitis, lithiasic migration, acute cholangitis), only after failed UDCA treatment should an indication of cholecystectomy be considered as an option [5].

In the event of extended intrahepatic lithiasis causing abscesses and repeated angiocholitis, interventional (endoscopic or radiological) treatment should be considered. It is aimed at: (1) permitting biliary drainage and (2) achieving clearance of intrahepatic lithiasis. Biliary drainage is carried out by placing a prosthesis or drain in the hepatic segments (or sectors) involved. Different endobiliary maneuvers using a Dormia or Fogarty occlusion catheter extract the calculi. And when calculi are numerous, large or impacted, use of a lithotrity apparatus is a possible option. Choledocoscopy is of major importance in interventional treatment. Choices of surgical approach and percutaneous or endoscopic radiology will be essentially dictated by considerations related to resources and local expertise.

In the event of failure or impossibility to achieve biliary drainage via a percutaneous or endoscopic approach, and notwithstanding optimal medical treatment, surgical treatment remains the reference [3,4]. It will be aimed at: (1) carrying out resection of the part of the liver responsible for the symptomatology and (2) achieving clearance of the bile ducts. While the relevant surgical principles emphasize parenchyma conservation, due to the topography of the intrahepatic biliary tree and the spread of lithiasis, they almost systematically involve anatomical resection (Fig. 3). While surgical treatment of LPAC syndrome presents no specificity, it represents treatment of complicated intrahepatic lithiasis. Preoperative testing for possible sepsis is indispensable. In the event of cholestasis, the bile ducts must be efficiently drained before surgical resection can ensue. During the operation itself, the main difficulties involve modified anatomical relations, which are associated with atrophy of the segments affected by lithiasis. While recurrence of intrahepatic lithiasis following surgery is not to be ruled out, it has never been reported in the literature. This positive finding is confirmed by our experience, and is probably due to the proper implementation of medical treatment by postoperative UDCA. Given the low risk of recurrence and the absence of constitutional abnormality of the bile ducts, there exists no recommendation on indications for biliodigestive anastomosis or bile duct access stoma. When hepatic resection cpreserves the biliary convergence, as a general rule our team does not carry out hepatico-jejunal anastomosis. This technique may be applied when complete clearance has not been achieved, in which case several subsequent endoscopy sessions are to be planned.

Surgical resection is also the curative treatment of choice in the event of neoplastic complications, particularly intrahepatic cholangiocarcinoma [4,6,10,23,25] (Fig. 9).

In the event of terminal liver failure with secondary biliary cirrhosis or massive intrahepatic lithiasis complicated by repeated bouts of sepsis, a liver transplant indication may be justified [3,7] (Figs. 4 and 6).

Patients undergoing liver transplant in the context of LPAC syndrome present no recurrence of symptoms. As a carrier of the donor's genome, the graft contains functional biliary carriers.

interventional treatment or hepatic surgery should be decided only by a multidisciplary team in an expert center.

Perspective

One perspective of current research involves a treatment potentially able of inducing increased activity of the ABCB4 gene [6,26].

Conclusion

A visceral surgeon is called upon to familiarize himself with LPAC syndrome. Indeed, he is often ''on the front line'' in cases of symptomatic lithiasis the time has come to indicate cholecystectomy. Any patient presenting elements suggesting this syndrome should be subjected to targeted investigations. Occurrence at a very young age should represent an alarm signal, as should recurrent biliary symptoms following cholecystectomy.

LPAC syndrome is easily treatable by means of a simple and effective medical treatment, ursodeoxycholic acid.

Present-day knowledge of this pathology has been enhanced by recent advances in molecular biology and may serve as an example of filiations between gene, protein, physiology and pathology.

Hepatic surgery in the context of LPAC syndrome is limited to the treatment of complications.

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The essential points

- The diagnostic criteria of LPAC syndrome are: onset of biliary lithiasis symptoms in a young adult (less than 40 years of age), recurrent biliary pain subsequent to cholecystectomy, typical radiological signs of intrahepatic lithiasis.
- LPAC syndrome is suggested in any lithiasis occurring in a patient less than 30 years of age presenting suggestive diagnostic orientation.
- LPAC syndrome is associated with a mutation of the ABCB4 gene, which codes for protein MDR3, biliary carrier of phosphatidylcholine.
- Diagnosis is based on association of two of the three diagnostic criteria. Genetic research or eventual testing on the genetic mutation is recommended.
- Treatment is based on ursodeoxycholic acid.
- Cholecystectomy should not be systematically performed but is recommended in cases of cholecystitis.
- Indications of epatic surgery remains limited to complicated forms (abscess, massive intrahepatic lithiasis, recurrent angiocholitis, neoplastic complications)

Disclosure of interest

The authors declare that they have no competing interest.

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