Radiology Case Reports 18 (2023) 11–16

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Low phospholipids associated cholelithiasis syndrome in a young women: A rare case report ☆

Amine Cherraqi, MD, Kaoutar Imrani, MD, Hajar Andour, MD, Ola Messaoud, MD, Khadija Benelhosni, MD, Nabil Moatassim Billah, MD, PhD, Ittimade Nassar, MD, PhD*

Central Radiology Department, CHU Ibn Sina, Rabat, Morocco

ARTICLE INFO

Article history:
Received 8 September 2022
Revised 18 September 2022
Accepted 21 September 2022

Keywords:
Cholecystectomy
Biliary pain
Intrahepatic lithiasis
LPAC syndrome
Imaging

ABSTRACT

Low phospholipid-associated cholelithiasis (LPAC) is a rare, still poorly understood genetic disorder characterized by the association of an ABCB4 mutation and low biliary phospholipid concentration with recurrent cholelithiasis, responsible for the development of intrahepatic lithiasis in adults. The mutation of the ABCB4 gene, which codes for the ABCB4/MDR3 ductal protein, a biliary transporter, leads to precipitation of cholesterol crystals in the bile ducts leading to the formation of intrahepatic stones. The diagnosis should be suspected when at least 2 of the following criteria are present: onset of symptoms before age 40; recurrence of biliary symptoms (biliary colic, jaundice, cholangitis, acute pancreatitis) after cholecystectomy; presence of echogenic foci in the liver indicative of intrahepatic stones or biliary sludge; previous episode(s) of intrahepatic cholestasis during pregnancy; and a family history of gallstones in first degree relatives. Imaging techniques, especially ultrasound, play an important role in the detection of intrahepatic stones. The majority of clinical situations are simple and not serious, often managed by medical treatment with ursodeoxycholic acid, but certain complicated forms may require more invasive endoscopic or surgical treatment. We report a case of a 43-year-old woman, cholecystectomized 5 years ago, who presented with liver colic-like pain with cytolysis and biological cholestasis. Ultrasound and MRI showed the presence of intrahepatic calculi disseminated along the bile duct pathway creating a comet tail appearance and generating a posterior shadow cone. The interrogation of the patient showed that her sister was being followed for LPAC syndrome. The diagnosis of LPAC syndrome was retained and the patient was put under medical treatment with ursodeoxycholic acid with regular clinical, biological and radiological follow-up.

☆ Competing Interests: The authors declare that they have no conflicts with this manuscript.

* Corresponding author.
E-mail address: Dr.amine.cherraqi@gmail.com (A. Cherraqi).

https://doi.org/10.1016/j.radcr.2022.09.072

Introduction

Low phospholipid-associated cholelithiasis syndrome (LPAC) is a recent syndrome first described in 2001 by Rosmorduc, Hermelin and Poupon at the Saint-Antoine Hospital in Paris [1]. It is a rare and peculiar form of intrahepatic cholestasis affecting mainly young adults, characterized by recurrent episodes of hepatic colic, acute cholangitis or pancreatitis, usually occurring after cholecystectomy [2]. It is often caused by a mutation in the MDR3/ABCB4 (multidrug resistance/ATP-binding cassette, subfamily B, member 4) class III gene, which encodes the bile duct protein MDR3. MDR3 (now known as ABCB4) is a member of the ABC superfamily of proteins. It is a flippase that acts by moving the phospholipid phosphatidylcholine from the inner leaflet to the outer leaflet of the canalicular membrane. From there, the phosphatidylcholine is flushed into the bile by bile acids [3,4]. This genetic mutation leads to a defective protein that is totally or partially unable to transport this major phospholipid into the bile, resulting in impaired solubilization of biliary cholesterol that precipitates as crystals in the intrahepatic bile duct and canaliculi [4,5]. LPAC syndrome is an elusive clinical entity and its prevalence remains unknown [6,7]. The diagnosis should be made when at least 2 of the following criteria are met:

- Onset of symptoms before the age of 40
- Recurrence of symptoms after cholecystectomy
- Presence of intrahepatic microlithiasis characterized by comet-tail artifacts, small hyper echoic foci, or biliary sludge on liver ultrasound [5].

Diagnosis and treatment of low phospholipid-associated cholelithiasis syndrome (LPAC) is easy, but the majority of cases are underestimated because they are not diagnosed [8]. We report a clinical case of a 43-year-old female patient with LPAC syndrome diagnosed after cholecystectomy.

Case report

A 43-year-old woman, who has undergone a cholecystectomy 5 years ago, presented with intermittent pain of the right hypochondrium in the form of hepatic colic, with no fever, vomiting or other symptom and did not improve under analgesics. At physical examination, there was an isolated discrete jaundice. Biological tests revealed a cytolysis associated with a cholestasis with aspartate aminotransferase (ASAT) 200 IU/L (normal: 0-35 IU/L), alanine aminotransferase (ALAT) 270 IU/L (normal: 4-36 IU/L), total bilirubin 26 mg/dL (normal: 0.1-1.2 mg/dL), direct bilirubin 15 mg/dL (normal: $\leq$0.3 mg/dL), alkaline phosphatase (ALP) 130 IU/L (normal: 35-104 IU/L), and gamma-glutamyltransferase (GGT) 340 IU/L (normal: 5-40 IU/L). Ultrasound showed hyperechoic intrahepatic formations, outlining the course of the intrahepatic bile ducts (IHBD), some of them with a discrete posterior shadow cone, others with a comet-tail artifact proving their cholesterolic character (Fig. 1). MRCPR (Magnetic resonance cholangiopancreatography) demonstrated IHBD microlithiasis in asignal on all the sequences, more marked in the segment V (Fig. 2), taking the appearance of an endoluminal defect (Fig. 3). The serological screening was negative including for viral hepatitis A, B, C, and E, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus (HIV). There was no abnormality in the immune status, in particular tests for (antinuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies, anti-neutrophil antibodies, anti-gp 210 cytoplasmic antibodies, anti-Sp100 antibodies, and IgG4 levels). The biological researches for an overload disease such as and hemochromatosis were normal. Extensive anamnesis revealed a story of LPAC syndrome in the sister. In the light of these data, the diagnosis of low phospholipid-associated cholelithiasis syndrome (LPAC) was retained. The patient was made under ursodeoxycholic acid (UDCA) with biological and radiological follow-up. The evolution was marked by a clinical improvement few weeks later.

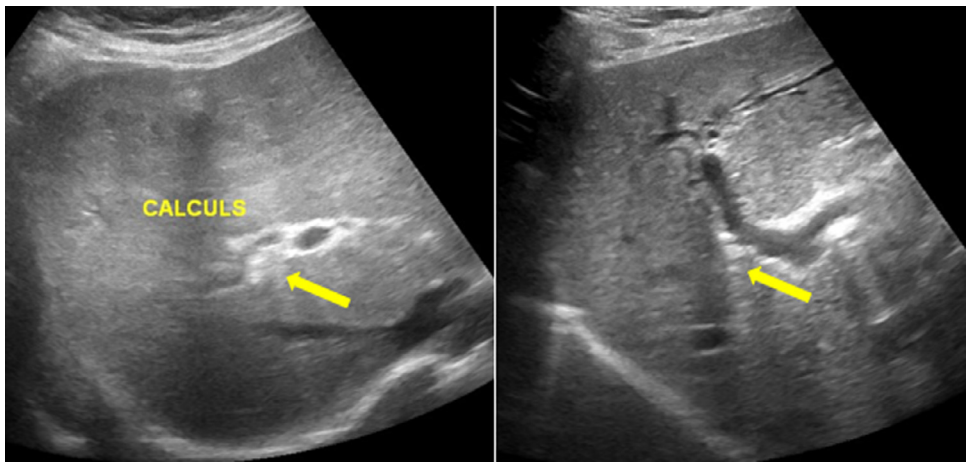

Fig. 1 – Hepatic ultrasound images in B mode showing the presence of hyperechoic intrahepatic formations, outlining the path of the intrahepatic bile ducts (IHBD), some of which describe a discrete posterior shadow cone, while others produce a comet-tail artifact testifying of their cholesterolic character.

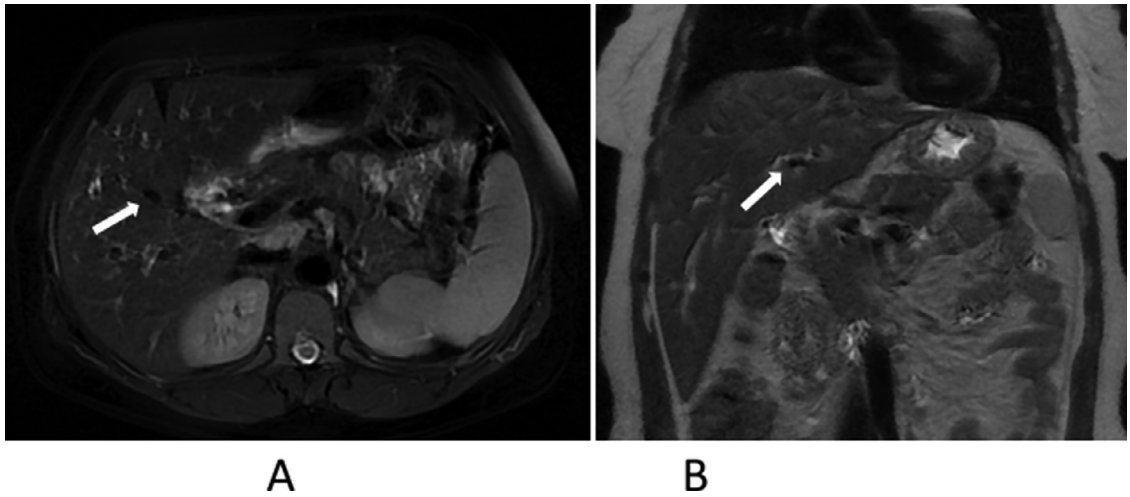

Fig. 2 – Axial sections of a Bili MRI in T2 (A), T1 (B and C) and 3D MRCPR (D) sequences showing intrahepatic bile duct (IHBD) microlithiasis in asignal, predominating at the level of segment V (arrows).

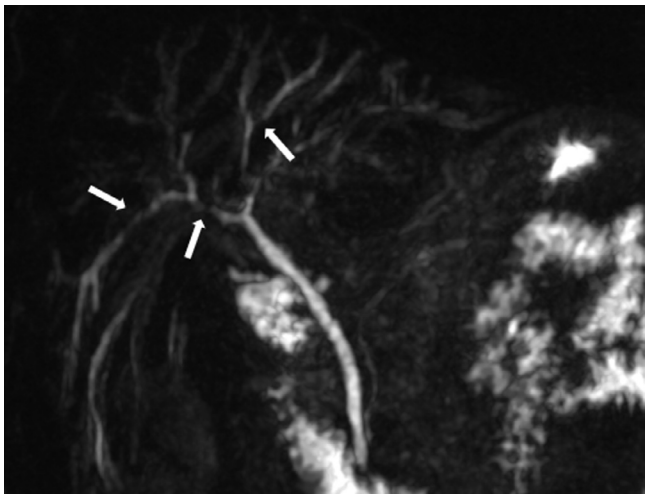

Fig. 3 – Image of a 3D Bili-MR sequence showing the presence of several endo-luminal defects in the intrahepatic bile ducts without upstream dilatation.

Discussion

LPAC (Low Phospholipid-Associated Cholelithiasis) syndrome, or genetic cholesterolic lithiasis, is a very particular form of biliary lithiasis that was first described in 2001 by the team of the Saint-Antoine hospital [1,9]. It is a genetic disease responsible of the formation of intrahepatic stones, characterized by the association of ATP-binding cassette subfamily B member4 (ABCB4) and a low level of bile phospholipids with symptomatic and recurrent cholelithiasis [8]. The prevalence of LPAC syndrome is unknown but considered quite low [6]. Some studies have estimated that LPAC syndrome accounts for approximately 1% of adult patients with symptomatic gallstone disease [2,10], another study showed that nearly a quarter of patients under 30 years of age admitted for symptomatic cholelithiasis have clinical and imaging features of LPAC syndrome [11]. It affects mainly women, with a sex ratio of about 1 / 3 [6,10,12] and the average age of onset of symptoms is 29.1 years in women and 38.7 years in men [12]. It is a disease of young adults, rarely seen in teenagers and exceptional in children [13].

The MDR3 (MultiDrug Resistance 3) protein, encoded by the ABCB4 gene, transports phosphatidylcholine which is the main phospholipid in human bile. These phospholipids, in association with bile acids, ensure the solubilization, the transport of cholesterol in bile and protect the biliary epithelium from the detergent effects of the hydrophobic physiological bile acids. A mutation of the ABCB4 gene, responsible for the dysfunction of the MDR3 protein, leads to a decrease in the concentration of biliary phosphatidylcholine. This deficiency is responsible of a decrease in cholesterol solubilization, a chronic damage in the biliary epithelium, an inflammatory reaction increasing GGT levels (Gamma Glutamyl transferase) and a precipitation of cholesterol in the various bile ducts (intrahepatic lithiasis) [1,4]. This diagram summarizes this pathophysiological process (Fig. 4) [9]. Genetic polymorphism is of great importance, we can distinguish: nonsense mutation, missense mutation, partial deletion of the gene, etc. [4,6,12,14]. One or more mutations in the gene are detected in only 50%-65% of patients with LPAC syndrome [4,6,12]. For patients without this mutation, several hypotheses have been put forward: mutation in unexplored regions of a gene (introns); -mutation on a promoter gene; mutation on a regulatory region; -mutation of another gene or biliary transporter (ABCB11 or BSEP, ABCC2, ABCG5/ABCG8, etc.); -synonymous mutation influencing gene production or regulation, etc. [4,6,12,15].

LPAC syndrome should be evoked when at least 2 of the following features are present: Onset of symptoms before age 40; recurrence of biliary symptoms (biliary colic, jaundice, cholangitis, acute pancreatitis) after cholecystectomy; presence of hyperechoic intrahepatic foci detected by ultrasound indicat-

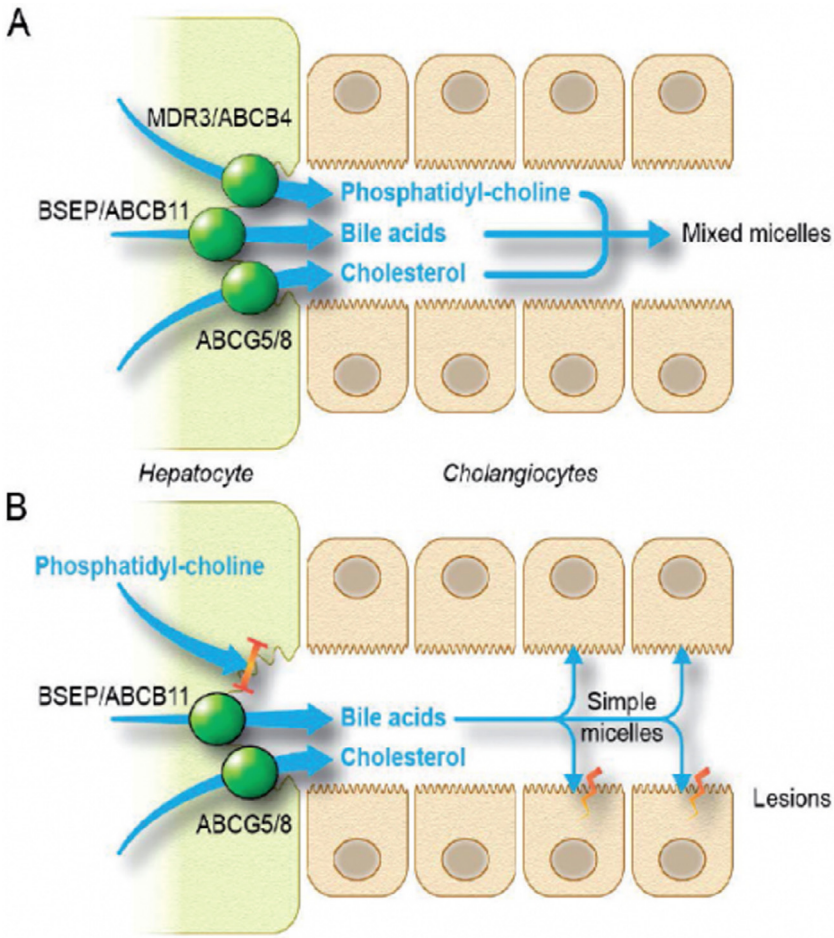

Fig. 4 – (A) Transporters of bile acids, cholesterol, and phosphatidyl choline (the major bile phospholipid) across the canalicular membrane of hepatocytes are normal. Mixed micelles are formed which allow the solubilization of cholesterol. (B) When the phospholipid transporter, the MDR3 protein encoded by ABCB4, is deficient, bile acids are transported without phospholipids and will form simple micelles that do not have the capacity to solubilize cholesterol. Microcrystals and cholesterol stones will then form. Moreover, bile acids transported without phospholipids have a detergent effect that will damage adjacent cholangiocytes.

ing intrahepatic stones or biliary sludge; previous episode(s) of gestational intrahepatic cholestasis; family history of gallstones in first-degree relatives and sensitivity to UDCA therapy [4–6]. The symbolic improvement of symptoms with UDCA therapy suggests that symptoms are not directly consequential to stones, but may also be consequential to inflammation of the IHBD and cholesterol crystals not detected by ultrasound [4]. A case-control study was performed in 2020 showed new clinical features associated with LPAC syndrome, including CBD (Common Bile Duct) lithiasis, normal patient weight, and no history of acute cholecystitis [2].

The diagnosis of LPAC syndrome is based on the above diagnostic criteria, radiological findings, biochemical analysis of bile collected by catheterization during duodenoscopy and on the search for mutation of the ABCB4 gene [6,9,11,12]. Bile analysis reveals a high cholesterol/phospholipid ratio [1,6], but it requires very specialized biochemical expertise and is difficult to perform. It cannot therefore be proposed as a confirmatory element in current practice. However, it should be noted that hyperechoic intrahepatic foci are observed in only about 80%-85% of patients with proven LPAC and the ABCB4 gene mutation is present in only 50-65% of cases [6]. This means that the absence of such foci and the mutation does not exclude the diagnosis [4,13].

Radiological examinations are of paramount importance to set the diagnosis of LPAC syndrome. These examinations must be performed and interpreted by a radiologist who is aware and informed of the diagnostic suspicion. The detection rate of radiological signs of the syndrome can vary from 90% (sensitized expert radiologist) to 5% (uninformed radiologist) [9]. In practice, ultrasound is the most relevant means to confirm the diagnosis. Indeed, in patients with LPAC syndrome with ABCB4 mutation, ultrasound detects typical "telltale" signs in 88%-95% of cases [9–12]. This high diagnostic relevance is also found in LPAC syndrome without ABCB4 mutation [12]. It shows intrahepatic hyper-echogenic spots responsible of comet-tail images which topography is compatible with microcrystal deposits along the biliary tree. Other imaging features are sludge, intrahepatic micro-lithiasis or macrocalculi with shadow cones [1,4,12,16]. Doppler ultrasonogra-

phy demonstrates colored comet-tail artifacts called "scintillating artifacts" testifying to microlithiasis [4]. The presence of numerous intrahepatic stones may be associated with dilatation of the intrahepatic bile ducts, not only proximal but also peripheral [13]. Most often, these radiological abnormalities typical of LPAC syndrome are not demonstrated by CT (Computed tomography) or MRI (Magnetic Resonance Imaging) of the liver. However, a complementary MRCP is necessary to document intrahepatic calculi, to reveal biliary dilatations and to rule-out other causes of intrahepatic lithiasis (mainly primary sclerosing cholangitis and Caroli disease, which represent the main differential diagnoses), the latter being mostly normal in case of LPAC syndrome [9].

LPAC syndrome may be associated with biological cholestasis, including high GGT levels that are likely related to chronic cholangiocyte injury [1,6].

Without treatment, the clinical course can be severe, with recurrent episodes of biliary pain (a clinical presentation suggestive of lithiasis migration associating pain and a fleeting increase in transaminases), cholangitis, jaundice, acute pancreatitis. Rarely, a saccular dilatation of the intrahepatic bile ducts molding the cholesteric lithiasis without underlying biliary stenosis and a gravid cholestasis in case of pregnancy can be seen. In addition, most often, there is no septic syndrome; therefore, no angiocholitis neither cholecystitis. Since in LPAC syndrome, intrahepatic lithiasis is symptomatic before vesicular lithiasis, cholecystectomy is often performed at a young age, preventing, thus, the risk of cholecystitis. Finally, despite the publication of exceptional cases of secondary biliary cirrhosis and cholangiocarcinoma [4], and although the long-term prognosis is not yet known, LPAC syndrome can be considered in the vast majority of cases to be non-serious if UDCA treatment is well followed [4,9,11,12,16].

LPAC syndrome is an excellent indication for prolonged medical treatment with UDCA at a dosage of 10 mg/kg/d (MA obtained in 2011 for this indication) [6]. This treatment increases the pool and the percentage of hydrophilic bile acids in the bile that protect the cholangiocyte membrane (and decreases the toxicity of hydrophobic bile acids). It also increases the expression of MDR3 protein and thus facilitates the secretion of phosholipids into the bile, leading to a better solubilization of cholesterol and, in long-term, to the dissolution of cholesterol crystals and stones. The other action of UDCA consists in inhibiting the inflammatory reaction through an attenuation of the expression of phospholipase A2-IIa induced by pro-inflammatory cytokines [4,17]. In the majority of cases, the symptoms disappear within the first few weeks of treatment. Ultrasound abnormalities disappear within months or even years [6]. This disparity between clinical and radiological symptom improvement may suggest that cholesterol crystals, which rapidly disappear from the bile during treatment, and/or associated inflammatory lesions play an important role in the development of symptoms. In case of failure in optimization of treatment with UDCA, adjuvant treatment with ezetimibe may be proposed on the basis of a pathophysiological mechanism, with no proofs of clinical efficiency [9]. In case of hypercholesterolemia, statins are preferable to fibrates, which increase cholesterol secretion into the bile. Finally, estrogen-progestin treatment should be stopped during the first few weeks of treatment with UDCA and as long as the disease remains symptomatic, as this treatment inhibits the secretion of phospholipids into the bile and thus increases the symptoms [9].

The effectiveness of medical treatment with UDCA allows the eviction of cholecystectomy in the majority of cases, since it does not prevent symptoms recurrence [6]. Cholecystectomy may be necessary in cases of gallbladder stones complicated by recurrent biliary colic or acute cholecystitis [4]. In some rare cases of intrahepatic stones with marked dilatation of the bile ducts, biliary drainage or even partial hepatectomy may be necessary if the patient presents with recurrent angiocholitis [9,16]. In complicated cases with biliary cirrhosis and permanent jaundice or ascites, liver transplantation should be considered [4].

A family screening by an ultrasound expert (and/or genotyping if an ABCB4 mutation has been demonstrated in the proband) can be proposed to first degree relatives over 18 years of age. In a young asyptomatic subject, a normal screening ultrasound may be repeated few years later because suggestive radiological signs may occur later. In asymptomatic parents with intrahepatic lithiasis, it is reasonable to propose treatment with UDCA [8,9].

Conclusion

LPAC syndrome represents about 1% of adult patients with symptomatic gallstone disease. Through this case, we clarify the clinical and radiological manifestations allowing to evoke the LPAC syndrome, to facilitate its early diagnosis, in order to improve its management and its evolution. The knowledge of LPAC syndrome, its precise diagnosis by ABCB4 genotyping and its treatment by UDCA offers to the patients a better long-term evolution with no recurrence, through an oral drug, avoiding liver surgery, which must be limited to the treatment of complications. Genotyping also allows family screening and treatment of asymptomatic patients before complications occur.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Patient consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

REFERENCES

[1] Rosmorduc O, Hermelin B, Poupon R. MDR3 gene defect in adults with symptomatic intrahepatic and gallbladder

cholesterol cholelithiasis. Gastroenterology 2001;120:1459–67.
[2] Dong C, Condat B, Picon-Coste M, Chrétien Y, Potier P, Noblinski B, et al. Low-phospholipid-associated cholelithiasis syndrome: prevalence, clinical features, and comorbidities. JHEP Rep 2020;3(2):100201.
[3] Fombuena B, Ampuero J, Álvarez L, Aparcero R, Llorca R, Millán R, et al. LPAC syndrome associated with deletion of the full exon 4 in a ABCB4 genetic mutation in a patient with hepatitis C. Rev Esp Enferm Dig 2014;106(8):544–7.
[4] Erlinger S. Low phospholipid-associated cholestasis and cholelithiasis. Clin Res Hepatol Gastroenterol 2012;36:S36–40.
[5] Rosmorduc O, Hermelin B, Boelle PY, Parc R, Taboury J, Poupon R. ABCB4 gene mutation-associated cholelithiasis in adults. Gastroenterology 2003;125(2):452–9.
[6] Rosmorduc O, Poupon R. Low phospholipid associated cholelithiasis: association with mutation in the MDR3/ABCB4 gene. Orphanet J Rare Dis 2007;2:29.
[7] Goubault P, Brunel T, Rode A, Bancel B, Mohkam K, Mabrut JY. Low-phospholipid associated cholelithiasis (LPAC) syndrome: a synthetic review. J Visc Surg 2019;156:319–28.
[8] Belabbes FZ, Benfaida A, Nawal B, El Idrissi Lamghari A, Rouibaa F. Low phospholipid-associated cholelithiasis: contribution of imaging in two cases. Cureus 2022;14(2):e22383.
[9] Condat B. Le syndrome LPAC (low phospholipid- associated cholelithiasis): mythe ou réalité? PostU FMC-HGE 2016:1–8. https://www.fmcgastro.org/textes-postus/postu2016-paris/le-syndrome-lpac-low-phospholipid-associatedcholelithiasis-mythe-ou-realite.
[10] Dong C, Condat B, Housset C, Poupon R, Zanditenas D, Chazouillères O, et al. Redéfinition des critères diagnostiques et estimation de la fréquence du syndrome LPAC. JFHOD 2018 [Poster no 562].
[11] Condat B, Zanditenas D, Barbu V, Hauuy M-P, Parfait B, El Naggar A, et al. Prevalence of low phospholipid-associated cholelithiasis in young female patients. Dig Liver Dis 2013;45(11):915–19.
[12] Poupon R, Rosmorduc O, Boëlle PY, Chrétien Y, Corpechot C, Chazouillères O, et al. Genotype-phenotype relationships in the low-phospholipid-associated cholelithiasis syndrome: a study of 156 consecutive patients. Hepatology 2013;58(3):1105–10.
[13] Goubault P, Brunel T, Rode A, Bancel B, Mohkam K, Mabrut J-Y. Low-phospholipid associated cholelithiasis (LPAC) syndrome: a synthetic review. J Visc Surg 2019;156(4):319–28.
[14] Pasmant E, Goussard P, Baranes L, Laurendeau I, Quentin S, Ponsot P, et al. First description of ABCB4 gene deletions in familial low phospholipid-associated cholelithiasis and oral contraceptives-induced cholestasis. Eur J Hum Genet 2012;20(3):277–82.
[15] Dröge C, Bonus M, Baumann U, Klindt C, Lainka E, Kathemann S, et al. Sequencing of FIC1, BSEP and MDR3 in a large cohort of patients with cholestasis revealed a high number of different genetic variants. J Hepatol 2017;67(6):1253–64.
[16] Poupon R, Arrive L, Rosmorduc O. The cholangiographic features of severe forms of ABCB4/MDR3 deficiency associated cholangiopathy in adults. Gastroenterol Clin Biol 2010;34(6–7):380–7.
[17] Ikegami T, Matsuzaki Y, Fukushima S, Shoda J, Olivier JL, Bouscarel B, et al. Suppressive effect of ursodeoxycholic acid on type IIA phospholipase A2 expression in HepG2 cells. Hepatology 2005;41:896–905.