Low Phospholipid-Associated Cholelithiasis (LPAC)

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7.1 Introduction

Low phospholipid-associated cholelithiasis (LPAC), synonym gallbladder disease 1, OMIN #600803, has been described firstly in 2001 as "intrahepatic and gallbladder cholesterol-cholelithiasis" due to a mutation of the ABCB4 gene which codes for protein MDR3 [1, 2]. It was later defined as a clinical syndrome characterized by at least two of the following criteria: (1) Age below 40 years at the onset of symptoms; (2) Recurrence of pain after cholecystectomy; (3) Intrahepatic echogenic foci or microlithiasis [3] (Fig. 7.1). There was also noticed a history of gallstones in first-degree relatives [2].

This is a rare condition, but it must be suspected in all cases of juvenile cholelithiasis. In fact, initially it had been considered responsible for less than 5% of symptomatic cases of gallstones [2, 4]. More recently it has been shown that LPAC affects up to 25% of women under 30 years of age with symptomatic cholelithiasis [5].

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Fig. 7.1 T2w Magnetic Resonance Cholangiography: multiple calculi within dilatations of intrahepatic biliary ducts in the right lobe and a pre-papillary common bile duct stone

7.2 Genetics

LPAC syndrome is associated with mutation of the *ABCB4* gene located on chromosome 7, locus 21 (7q21) which codes for protein MDR3 [1, 3]. MDR3 is a phospholipid floppase responsible for transport of phospholipids into bile. As consequence of the altered gene product a reduced concentration of phospholipids is present into bile, thus a decreased amount of phosphatidylcholine is excreted in the bile canaliculi. In the absence of phosphatidylcholine there is an impaired solubilization of cholesterol through the micelles which become unstable. As consequence, the cholesterol precipitates and forms calculi.

Indeed, the reduced concentration of phosphatidylcholine is responsible for the development of a wide range of cholangiopathies, from infancy to the adulthood (Table 7.1). The typical hallmarks of this disorder in infancy include high levels of gamma-glutamyl-transferase (GGT) and the typical markers of cholestasis [6–8]. It is noteworthy that hepatocellular carcinoma and intrahepatic cholangiocarcinoma have been documented in patients with *ABCB4*/MDR3 mutations. [9].

In a study including 156 patients with LPAC, a genetic variant of *ABCB4* gene was only found in 50% of cases; clinical features were similar in the groups with and without these variants, suggesting that unexplored regions of the gene or different genes could be involved [10]. Mutations are mostly heterozygous frameshift, nonsense or missense, but homozygous missense mutations have also been reported.

Table 7.1 Disease spectrum of MDR3 mutations

Childhood
• Neonatal cholestasis
• Progressive Familial Intrahepatic Cholestasis 3 (PFIC3)
Adulthood
• Low phospholipid-associated cholelithiasis (LPAC)
• Intrahepatic cholestasis of pregnancy (ICP)
• Drug-induced cholestasis
• Progressive Familial Intrahepatic Cholestasis 3 (PFIC3)

Indeed, a heterozygous *ABCB4* mutation has been detected in a woman who developed choledocholithiasis in adolescence, followed by cholestasis of pregnancy, and finally biliary cirrhosis at the age of 47 [11]. LPAC has also been described in two siblings with combined features with progressive familial intrahepatic cholestasis (PFIC) 3 [12]. However, the association between LPAC and biliary cirrhosis is rare, and patients presenting with the LPAC phenotype are not at particular risk of developing biliary cirrhosis later in adulthood.

Several hypotheses have been suggested to explain the lack of mutations in ABCB4 gene in patients with LPAC [13]: (1) Mutation in unexplored region of a gene (introns); (2) Mutation on a gene promoter; (3) Mutation in a regulatory region; (4) Mutation of another gene or another biliary carrier (*ABCB11* or *BSEP*, *ABCC2*, *ABCG5*/*ABCG8*, etc.); (5) Synonymous mutation influencing production or regulation of the gene.

7.3 Clinical Characteristics

LPAC syndrome affects generally young adults, with a female/male ratio of 3:1 [10]. In the large French cohort of 156 patients, the mean age at the onset of symptoms was 38.7 years for men and 29.1 years for women [10]. The onset in childhood and adolescence is quite uncommon [14]. The biliary stones present in LPAC syndrome are yellow and saturated with cholesterol in consequence of the elevated cholesterol/phospholipid ratio in the bile. By comparison, gallstone disease is frequent as high as 10% in the general population, with a prevalence rate >50% at 50 years of age in both men and women (Table 7.2, ref. 15). Gallstone disease is frequently associated to metabolic syndrome, and the rate of gallstone disease increases with advancing age, and in 20% of cases there are symptoms of disease or complications [15].

The clinical hallmark of LPAC syndrome is biliary pain leading to cholecystectomy in 90% of cases [3], due to residual intrahepatic lithiasis, Oddi dysfunction, or residual lithiasis in the common bile duct. After cholecystectomy there is also a recurrence of acute cholangitis, or pancreatitis, due to intrahepatic lithiasis or lithiasis migration [3]. Indeed, intrahepatic lithiasis can predispose to recurrent cholangitis and eventually to secondary biliary cirrhosis as a consequence of the aggression

Table 7.2 Clinical characteristics of LPAC syndrome in comparison with classical gallstone disease

	LPAC syndrome	Classical gallstone disease
Age at onset of symptoms	Before 30 years	After 45 years
Associate conditions	Conditions linked to *ABCB4* mutations	Metabolic syndrome
Female/male ratio	3:1	1.5:1
Family history	Symptomatic intrahepatic lithiasis in first-degree relatives	Gallstones frequent in relatives
Imaging	Gallstones and intrahepatic lithiasis	Gallstones
Intrahepatic cholestasis of pregnancy (female patients)	50% of cases	Rare
Complications (pancreatitis, cholangitis, migration of calculi)	Frequent	Rare
Recurrence of pain after cholecystectomy	Frequent	Very rare

of hydrophobic bile acids [3, 10, 16]. The differential diagnosis includes congenital abnormalities of the biliary tree, i.e. Caroli disease, primary and secondary sclerosing cholangitis, and cholangiocarcinoma.

About 50% of women with LPAC syndrome who became pregnant do experience intrahepatic cholestasis of pregnancy (ICP) [10]. This condition is characterized by cholestasis, itching, and altered liver function tests mostly in the third trimester of pregnancy [17]. Another possible association is the drug-induced cholestasis following administration of amoxicillin, clavulanic acid, and risperidone [18]. Moreover, patients with a MDR3 mutation have a threefold increased risk of cholestatic drug-induced liver damage from oral contraceptives, psychotropic drugs, proton-pump inhibitors, and some antibiotics [18]. The phenotype of PFIC3 rarely associated with LPAC is caused by several biallelic variations (≥70% missense) [19].

7.4 Diagnosis

Ultrasound examination may detect gallstones and intrahepatic stones that appear as heterogeneous and echoic foci centred on the intrahepatic ducts, or as "comet-tail artefact" [20]. Magnetic resonance cholangiopancreatography (MRCP) shows the presence of intrahepatic stones and eventually, mild or moderate dilations. Such dilations may be present in one or two segments, or may be diffuse.

To confirm the diagnosis, ABCB4 genotyping is recommended in the index case and in the first-degree relatives.

7.5 Treatment

Standard therapy consists in ursodeoxycholic acid (UDCA) administration (13–15 mg/kg/day) which is beneficial for symptoms of disease. UDCA has several mechanisms of action including (1) protection of injured cholangiocytes against toxic effect of bile acids; (2) stimulation of impaired biliary secretion; (3) stimulation of detoxification of hydrophobic bile acids; (4) inhibition of apoptosis of hepatocytes [21]. Actually, no further agent is recommended in the management of LPAC. Nevertheless, on the experimental point of view two new medications might be used in the future for this condition. Interestingly, 24-ursodeoxycholic acid (*nor*-UDCA), a derivative of UDCA has been found highly effective in the mouse model of knockout mice (*Abcb4*$^{-/-}$) that closely reproduce the human cholangiopathies, such as PFIC3 and primary sclerosing cholangitis (PSC); in such animal model it has been shown to have superior anti-inflammatory, anti-fibrotic, and anti-proliferative effects compared to UDCA [22]. Recently, *nor*-UDCA has been successfully tested clinically in patients with PSC [23], thus it might have a potential indication also for patients with LPAC. Moreover, an engineered fibroblast growth factor 19 (FGF19), variant NGM282 has been assayed in murine model deficient in Mdr2 [24]. This agent produced remarkable effects on liver enzymes, liver histology, and bile acid homeostasis. Up to now, the engineered NGM282 has been tested in a phase 3 clinical trial for primary biliary cholangitis [25] but has a potential background to be translated also to patients with LPAC.

Cholecystectomy is indicated in case of symptomatic gallstones. However, bile stone recurs in many cases after cholecystectomy, thus endoscopic retrograde cholangiopancreatography (ERCP) should be performed. Moreover, rarely major liver surgery should be performed. The surgical approach for intrahepatic calculi should be individualized. Due to the expected need for long-term access to the intrahepatic biliary ducts, procedures such as hepatic-cutaneous jejunostomy with subcutaneous access loop have been proposed [26]. In case of complications, i.e. hepatic atrophy, abscesses, large intrahepatic stones, and malignancy, surgical resection may be appropriate. Patients with end-stage liver disease may be candidates for liver transplantation.

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