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Clinical Characteristics and Genetic Analysis of Low-Phospholipid Related Cholelithiasis Stone Syndrome

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Abbreviations:

CHP: Cirrhosis and Portal Hypertension; ACMG: American College of Medical Genetics and Genomics; GGT: Gamma-Glutamyl Transferase; ICP: Intrahepatic Cholestasis of Pregnancy; LPAC: Low Phospholipid Associated Cholelithiasis; MDR3: Multi-Drug Resistant 3; PIFC3: Progressive Familial Intrahepatic Cholestasis type 3; VUS: Variants of Uncertain Significance; UDCA: Ursodeoxycholic Acid

1. Abstract

1.1. Background & Aims

This study aimed to explore the clinical characteristics, imaging examinations and genetic features of patients with Low Phospholipid-Associated Cholelithiasis Syndrome (LPAC), and to improve the understanding of this disease. Methods: A retrospective analysis was conducted on 5 patients diagnosed with LPAC by genetic testing who were hospitalized in the Department of Infectious Diseases of the Fifth Medical Centre of the PLA General Hospital from January 2015 to December 2025. The clinical characteristics, imaging examinations, genetic features and clinical outcomes of the patients were summarized. The gene mutation detection of the probands was performed using next-generation sequencing of the whole exome. Sanger sequencing was conducted in the family for verification, and the pathogenicity of the new mutation site was evaluated.

1.2. Results

Among the 5 patients with LPAC, 1 had a biallelic mutation and 4 had a single-allelic mutation. Among them, the patient with a biallelic mutation was diagnosed with LPAC (overlapping ICP) due to carrying a benign mutation. At the onset of the disease, the incidence of abnormal liver function in the patients was 100% (5/5), 100% had elevated GGT (409.8±614.9) U/L, 40% (2/5) had elevated DBIL, and 100% (5 cases) presented with cholestasis. All patients had a history of cholecystectomy and liver fibrosis. Three cases presented with liver cirrhosis, splenomegaly and portal hypertension. All patients underwent liver pathological examination. Three cases (60%) were suggested to have liver cirrhosis. The characteristics included small bile duct hyperplasia in 80% (4/5), bile duct absence in 20% (1/5), portal area fibrosis in 100% (5/5), positive CK7 expression in 100% (5/5), and positive copper staining in 20% (1/5). All 5 patients were given ursodeoxycholic acid treatment. The average follow-up time was 8.8 (7-15.6) years. The conditions of 2 cases gradually progressed (1 case of liver cancer and 1 case of liver failure), while the conditions of the remaining 3 cases were still stable. A total of 6 ABCB4 gene mutation sites were detected in 5 patients, including 4 missense mutations and 2 small fragment deletions. Three new mutations were identified: c.2301del (p.Phe767LeufsTer30) was rated as suspected pathogenic. c.1241G>T (p.G414V) and c.2394+82C>T (intron) are variations of unknown clinical significance (VUS). Computer simulation predicted that c.1241G>T (p.G414V) was a harmful mutation and c.2394+82C>T (intron) was a benign mutation.

1.3. Conclusions

LPAC patients mostly occur in young adults, caused by a single gene mutation of ABCB4, and more often develop gallbladder stones and undergo cholecystectomy in adulthood. If young adults with abnormal transaminase levels accompanied by elevated GGT and gallbladder stones are clinically found, this disease should be considered. Genetic testing should be conducted as soon as possible for a confirmed diagnosis. The application of UDCA treatment can improve prognosis and reduce surgical treatment.

1.4. Impact and Implications

Low Phospholipid-Associated Cholelithiasis Syndrome is rarely seen in clinic. This study introduced the specific clinical characters in Low Phospholipid-Associated Cholelithiasis Syndrome. This study can improve clinicians' understanding of PLAC and reduce the misdiagnosis rate in clinical practice.

2. Introduction

Low Phospholipid-Associated Cholelithiasis Syndrome (LPAC) is a rare hereditary intrahepatic gallstone disease, closely related to the reduced secretion of phosphatidylcholine in bile [1]. This disease is caused by a single heterozygous mutation in the ABCB4 gene and is an autosomal recessive inheritance. It was first reported by the Raoul Poupon team in 2001 [1]. It is more prevalent in young adults [2]. The exact prevalence is not yet clear, but it is estimated that it accounts for approximately 1% of patients undergoing cholecystectomy [3]. The clinical features are symptomatic and recurrent cholelithiasis, often accompanied by liver fibrosis. If the condition is not controlled, it is prone to develop into end-stage liver diseases such as liver cirrhosis. Biochemical tests and liver histopathology were similar to PFIC3, with elevated serum gamma-glutamyl transpeptidase (γ-GGT) and significant small bile duct hyperplasia observed [4]. The main pathological features of the gallbladder were reduced secretion of phosphatidylcholine in bile and cholesterol supersaturation. This study analyzed the clinical characteristics, imaging examinations and gene mutations of 5 patients with LPAC admitted to the Department of Infectious Diseases of the Fifth Medical Centre of the Chinese People's Liberation Army General Hospital from January 2015 to December 2025, aiming to enhance the understanding of this disease.

3. Patients and Methods

3.1. Patients

Five patients admitted to the Department of Infectious Diseases at the Fifth Medical Centre of PLA General Hospital between January 2015 to December 2025, who were clinically, radiologically, pathologically, and genetically diagnosed with LAPC, were included in this study. Clinical and auxiliary examination data for all patients were collected, including gender, age, clinical symptoms, blood biochemistry, imaging findings, liver pathology, ABCB4 genotyping, and mutation sites. All five patients returned for follow-up visits or were followed up by telephone, and their clinical outcomes were recorded.

3.2. Diagnostic Criteria

Diagnostic criteria: According to the diagnostic indicators for LPAC [5], including at least two of the following three major criteria: (1) onset of biliary symptoms before age 40; (2) persistence of biliary symptoms after cholecystectomy; (3) ultrasound evidence of intrahepatic (micro)stones. Minor diagnostic criteria: family history of gallstones in young individuals (<40 years) or personal or family history of ICP [4]. A diagnosis can also be made if only one major LPAC criterion is met, provided two related minor criteria are present. Criteria for cholestasis include serum direct/conjugated bilirubin >1.0 mg/dL (17 μmol/L), or serum alkaline phosphatase (ALP) >1.5 times the upper limit of normal (ULN), and gamma-glutamyl transferase (γ-GGT) >3 times the ULN. Significant liver fibrosis is defined as a Metavia histological score greater than 2. Chronic cholestasis is considered when cholestasis persists for more than 6 months [6], and cirrhosis is diagnosed according to the 2019 "Guidelines for Diagnosis and Treatment of Cirrhosis" [7].

3.4. Genetic Testing and Mutation Analysis

This study was approved by the Ethics Committee of the Fifth Medical Centre of PLA General Hospital (KY-2023-9-57-1). After the patients and their parents signed the informed consent form, 2.5-3.0 ml of venous blood was drawn from the patients and their parents and placed in EDTA anticoagulation tubes. The blood samples were sent to Beijing Benjamin Genetic Testing Service Company. The whole blood genome was extracted using the QIAamp@ DNA Mini kit (QIAGEN Company in the United States). The second-generation sequencing of the entire exome of liver disease-related genes was used to sequence the genomic DNA of the patients. For some patients with positive mutations in the ABCB4 gene, Sanger sequencing was used for parental verification. The new mutations were predicted for their harmfulness using SIFT, PolyPhen-2, PROVEAN, and Mutation Taster software. The amino acid conservation of the ABCB4 homologous protein sequences of different species was analyzed using Clustal Omega. The pathogenicity of the variations was evaluated according to the "Guidelines and Standards for Classification of Genetic Variations and Standards" issued by the American Society of Human Genetics and Genomics in 2015.

3.5. Statistical Method

Simple statistical analysis was conducted using SPSS 19.0 software. Count data were expressed as frequencies and percentages (%), while measurement data that followed a normal distribution were presented as $\bar{x} \pm s$, and those with a skewed distribution were represented as M (Q1, Q3).

4. Results

4.1. General Information

A total of 5 patients with LPAC were included, including 4 males and 1 female. The median age at onset was 25 (19, 37) years old. None of the parents of the 5 patients had consanguineous marriages. One patient's father had died of liver cirrhosis, his son. one sister and the sister's son. another sister's son, all the had abnormal liver functions. One patient's sister died of "liver cirrhosis".

4.2. Clinical Manifestations and Biochemical Results

Among the 5 patients with LPAC, 2 cases (40%) presented with liver cirrhosis; 2 cases (40%) sought medical attention due to jaundice; and 1 case (20%) visited the hospital due to abnormal liver function without any symptoms.

The γ-glutamyl transpeptidase levels were elevated in 5 patients at the initial diagnosis, ranging from (409.8±614.9) U/L. Among them, 3 patients (30%) had elevated alanine aminotransferase, 3 patients (30%) had elevated aspartate aminotransferase, 4 patients

(40%) had elevated total bilirubin, 2 patients (20%) had elevated direct bilirubin, and 3 patients (30%) had elevated total bile acid. Three patients (30%) presented with chronic cholestasis (Table S1).

4.3. Imaging Examination

All 5 patients with LPAC had gallbladder stones or common bile duct stones when they were young (< 40 years old), and underwent cholecystectomy. The median age at cholecystectomy was 29 years (Table2). Patient one, mild dilation of the bile duct occurred shortly after cholecystectomy (see Figure 1); patient two was LPAC (with overlapping ICP), and intermittent biliary symptoms occurred after cholecystectomy, which were tolerable; patient three progressed to hepatocellular carcinoma (Figure 1); patient four had the mildest condition, with no obvious symptoms after cholecystectomy; patient five still felt discomfort in the right upper abdomen more than 10 years after cholecystectomy.

4.4. Pathological Characteristics

Five patients (100%) underwent liver tissue pathological examination. The pathological features included 80% (4/5) of small bile duct hyperplasia, 20% (1/5) of bile duct absence, 100% (5/5) of portal area fibrosis, 100% (5/5) of positive CK7 expression, 20% (1/5) of copper staining positive, suggesting 60% (3/5) of liver cirrhosis (see Table 3). Patient one was a male, 23 years old. The first liver tissue pathological examination was G2S1 (bile duct absence, positive CK7 staining, mild fibrosis in the portal area, and decreased expression of CD10 in some areas), and at that time, bile duct stones were found, and a cholecystectomy and bile duct resection were performed. The pathological result of the stones suggested them to be sand-like and cholesterol-like stones. Patient two had liver tissue pathology showing bile duct disappearance (Figure 2).

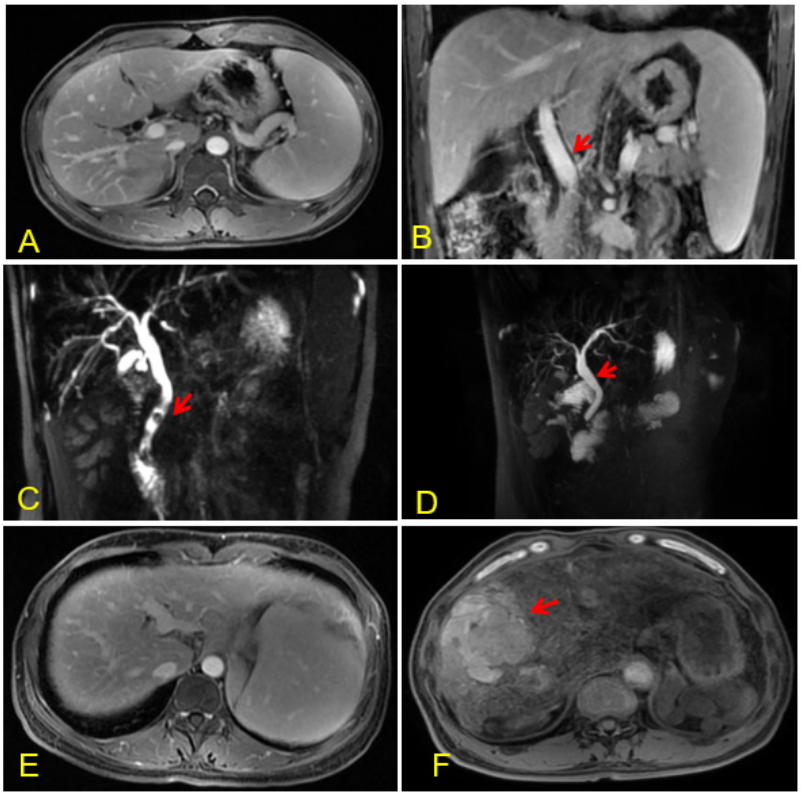

Figure 1: A-D (Patient 1), A: Abdominal ultrasound in August 2018 did not show any definite gallbladder stones. B: Abdominal MRI indicated mild dilation of intrahepatic bile ducts and common bile duct. C: MRCP in January 2019 showed multiple stones in the common bile duct. D: MRCP in August 2020 showed mild dilation of intrahepatic and extrahepatic bile ducts (one year and more after gallbladder removal). E: Patient 2 showed mild dilation of intrahepatic bile ducts (8 years after gallbladder removal). F: Patient 3 progressed to hepatocellular carcinoma (27 years after gallbladder removal).

Table 1: Imaging examinations of 5 patients with LPAC.

Patient No	Gender	Age (Y)	Age (Y) cholecystectomy	Now age(Y)	LPAC	Overlap ICP （N）	Imaging	UDCA response
1	M	23	24	31	Yes	—	splenomegaly	PR
2	F	35	35	43	Yes	2	Cirrhosis, splenomegaly portal hypertension	PR
3	M	29	29	56	Yes	—	Cirrhosis, portal hypertension	PR
4	M	19	19	57	Yes	—	Liver echo thicken	CR
5	M	18	38	52	Yes	—	Cirrhosis, portal hypertension	PR

PR: partial response ; CR: complete response.

Table 2: Characteristics of liver histopathology and immunohistochemical staining in 5 patients with LPAC.

Patient NO	Bile duct injury	Fibrosis of the sink area	Grade (G) Fibrosis (S)	CK7	CU
1	Reduced interlobular bile duct, bile duct epithelium injury, small bile duct hyperplasia	YES	G2S1	YES	-
	The epithelium of the interlobular bile duct was atrophic and lost, typical interlobular bile duct was rare, and small bile duct hyperplasia was obvious	YES	G2S2	YES	-
2	Ductopenia	YES	G1S3-4	YES	+
3	Small bile duct hyperplasia	YES	G3S4	YES	-
4	The epithelium of the interlobular bile duct is atrophic and absent, and the small bile duct is hyperplasia	YES	G1S2	YES	-
5	Small bile duct hyperplasia	YES	G3S4	YES	-

-, Negative; +, Positive;.

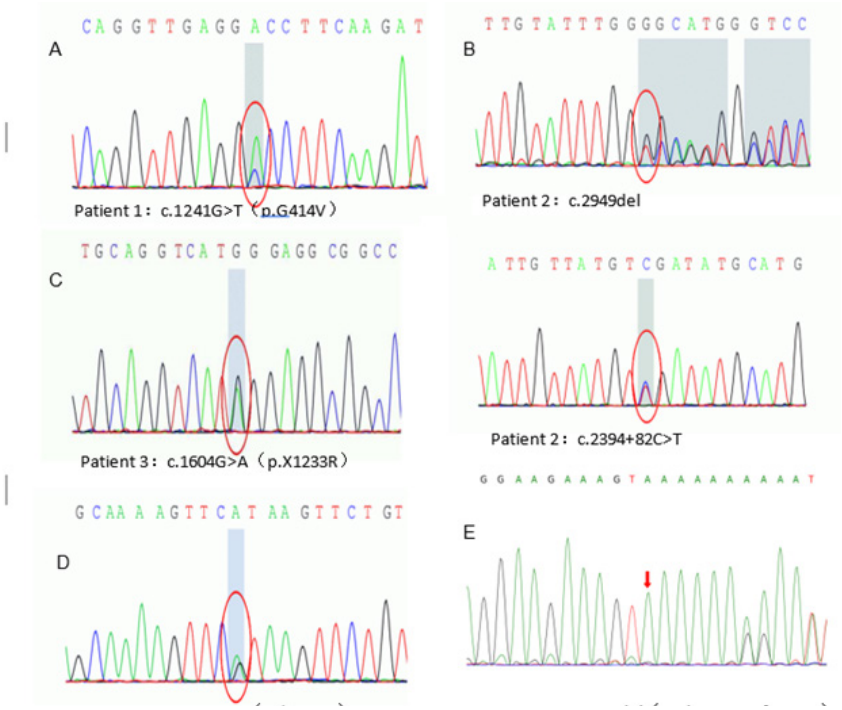

Figure 2: Sanger sequencing graphs of the examined sites for 5 patients with LPAC.

4.5. Gene Mutation Analysis

Among the 5 LPAC patients, 4 had single heterozygous mutations in ABCB4, and 1 had a compound heterozygous mutation (with one of the sites being a benign mutation and the clinical diagnosis being LPAC with overlapping ICP). Among the 5 patients, two cases (patient 1 and patient 2) underwent parental verification. one of them was from the mother, and another was from both parents. Three cases (patient 3, patinet 4 and patine 5) did not undergo parental verification due to their advanced age. Among these two cases (patient 4 and patient 5), both of their sons had carried the same mutant gene as them, and their liver functions were abnormal, with elevated γ-GGT, and they have been taking UDCA treatment. The son of patient four now has mild gallbladder stones, while the son of patient five is young and no gallbladder stones have been found. Close follow-up is needed to understand if cholesterol stones will appear in the child's growth process in the future. Among the 5 LPAC patients, there were 3 types of missense mutations, all of which were reported to be pathogenic. There were 2 types of deletion mutations and 1 type of splicing mutation (Figure 2).

By consulting the Human Gene Mutation Database, the ClinVar disease database and domestic and foreign literature, it was found that three mutation sites were not reported in the HGMD database. These were considered to be new mutations. According to the ACMG rating guidelines, the unreported sites were rated. The mutation site c.2301del (p. Phe767LeufsTer30) was rated as likely pathogenic (LP). The VUS sites were c.1241G>T (p.G414Y) and c.2394+82C>T. Using software such as Mutation Taster, PolyPhen-2, FATHMM-MKL, CADD, Varseak, Splice AI, SIFT and FATHMM-indel to predict the pathogenicity of the VUS sites, site c.2394+82C>T was benign, while site c.1241G>T (p.G414Y) showed that the mutation was harmful (Table S4).

4.6. Treatment, Follow-Up and Prognosis

Among the 5 patients with LPAC in this study, all were treated with liver-protective, enzyme-lowering and jaundice-reducing med-

ications during their hospitalization, including Compound Glycyrrhizin, Ursodeoxycholic Acid Capsules, Injection of Dibutyryl Sulfamate Methionine, and Cholic Acid. The median follow-up time was 8.8 (7 - 15.6) years. In patient two and patient three, the onset was liver cirrhosis, and the bile stasis progressed slowly. After UDCA treatment, the condition was relatively stable, but patient three gradually progressed to liver cancer, and is currently receiving conservative treatment. In patient five, the onset suggested early liver cirrhosis, with an unclear cause. Later, the condition gradually progressed to the decompensated stage of liver cirrhosis combined with ascites, liver encephalopathy, etc. After then, genetic testing indicated a single heterozygous mutation of ABCB4, confirming the diagnosis of LPAC. Long-term application of UDCA maintained relatively stable liver function indicators. Patient one was younger than the other patients. At the age of 19, a bile duct stone was found, and genetic testing indicated a single heterozygous mutation of ABCB4, confirming the diagnosis of LPAC. Due to obvious biliary symptoms, a cholecystectomy and partial bile duct resection were performed. After the operation, UDCA was taken orally continuously. Multiple liver function tests showed slightly elevated GGT, while other liver enzymes were normal. Imaging examinations indicated that the common bile duct had again shown mild dilation. Currently, the condition is relatively stable, and close follow-up observation is ongoing. Patient four was diagnosed with gallbladder stones at an early stage and underwent cholecystectomy. After the operation, continuous UDCA treatment was given, and no obvious biliary symptoms occurred again. The condition was stable. Patient four and patient five each had one child, both carrying the same gene as their fathers. The child of patient four (currently 31 years old) has mild gallbladder stones and cholecystitis, accompanied by mild liver function abnormalities (GGT elevated), and is under follow-up observation. It is considered possible to be LPAC. The son of patient five is younger and currently has abnormal liver function, without showing gallbladder stone manifestations, and is also under close follow-up observation.

Among the 5 LPAC patients in this study, most had single heterozygous mutations in ABCB4. The overall condition of these patients was milder compared to those with double allelic mutations. However, the prognosis of this group of patients also varied, which was believed to be related to the type of their genetic mutations. For instance, patient five had a deletion mutation, and the disease progressed severely. It was considered that the clinical phenotype of the deletion mutation was relatively more severe.

5. Discussion

The ABCB4 gene is located on chromosome 7 (7q21) and encodes multidrug resistance protein 3 (MDR3). MDR3 is a membrane-bound P-glycoprotein belonging to the ATP-binding cassette (ABC) transporter superfamily. In the liver, it transports phosphatidylcholine (PC) from the inner leaflet to the outer leaflet of the bile canalicular membrane, thereby forming bile [1]. Mutations in the ABCB4 gene can lead to a functional deficiency of the MDR3 protein, resulting in reduced secretion of phospholipids into bile. This impairs the formation of mixed micelles comprising cholesterol, bile acids, and phospholipids-which are the primary carriers for cholesterol solubilization. Consequently, bile becomes highly lithogenic, containing high concentrations of cholesterol crystals that precipitate within bile ducts, leading to the formation of intrahepatic and extrahepatic cholesterol stones. Due to excessive bile acid secretion, the bile also exhibits strong detergent properties, causing inflammation of biliary epithelium and elevated gamma-glutamyl transferase (GGT) levels produced by bile duct cells [8].

ABCB4 gene mutations can lead to a wide range of clinical phenotypes. Progressive familial intrahepatic cholestasis type 3 (PFIC3) was the most severe which caused by biallelic ABCB4 mutations. This condition typically presents in late infancy, adolescence, or even young adulthood with cholestasis or cirrhosis accompanied by portal hypertension. Heterozygous ABCB4 mutations may be associated with milder clinical phenotypes, such as neonatal transient cholestasis (TNC), drug-induced liver injury (DILI), low phospholipid-associated cholelithiasis syndrome (LPAC), and intrahepatic cholestasis of pregnancy (ICP) [9-11]. Literature reports [12] indicate that 30% to 50% of patients presenting with LPAC syndrome harbour pathogenic ABCB4 mutations, highlighting the genetic heterogeneity of this disease and suggesting the likely involvement of other contributing factors—genetic, congenital, or environmental [2]. Pathogenic ABCB4 mutations are classified into two main categories: large-scale variants (such as nonsense or frameshift mutations), designated as class I, which result in protein absence; and missense variants, categorized into classes II to V, leading to defects in MDR3 protein maturation (class II), functional activity (class III), stability (class IV), or interaction with partner proteins (class V) [8].

The LPAC syndrome is typically diagnosed in young adults, with a median age of diagnosis being 36 years old and the median age of symptom onset being 27 years. This indicates a significant delay in diagnosis, and occasionally, delayed cases have been observed (15% of cases were diagnosed after the age of 40). In this study, the median age of onset for the 5 patients was 25 years old, and the diagnosis age was all delayed, similar to the reports in the literature [12]. This disease is relatively rare in infants but may occur during adolescence. The sons of the two patients in this study both carried the same gene mutation as their fathers, and one of them has already developed mild gallbladder stones, while the other is younger and currently has mild liver function abnormalities, with the possibility of developing gallbladder stones and gallbladder inflammation in the future. There have been reports that the proportion of LPAC in females is significantly higher than that in males (approximately 3:1). It is considered that the female gender may have a potential role in the risk of gallstones, as well as the inhibitory effect of female sex hormones on bile transport proteins (especially MDR3). Among women with LPAC syndrome, the prevalence of pregnancy-induced intrahepatic cholestasis of pregnancy (ICP) is higher. In this study, there was only one female with LPAC syndrome, and she also had ICP, which may be related to the small sample size. Further observation with an expanded sample size is

considered. Overall, the estimated prevalence of LPAC in the general population is 10-40 per 100,000 people, but the incidence of LPAC syndrome in young patients with symptomatic gallbladder stones may be higher than 25% [13-16].

The clinical manifestations and imaging examinations of LPAC are similar to those of typical gallstone diseases. The characteristic symptoms include severe biliary colic, occasionally accompanied by biliary complications such as common bile duct stones, acute cholangitis, or acute pancreatitis. Usually, biliary pain occurs in patients under forty years old, without other related risk factors for gallstones. Biliary pain persists even after cholecystectomy, which strongly suggests LPAC syndrome. Among the five patients in this study, all experienced significant biliary colic before the age of forty and underwent cholecystectomy. Three of them were diagnosed with liver cirrhosis at the onset of the disease, and one felt discomfort in the right upper abdomen for many years after the surgery, with imaging suggesting intrahepatic bile duct dilation. One patient overlaps ICP, and another patient gradually progressed to liver cancer over time, and one patient had a relatively mild condition with relatively stable liver function. Some literature suggests that there is a family history of gallstones in the first-degree relatives, while this proportion is 34% in typical gallstone diseases. Apart from gallstones, liver biochemical indicators usually indicate an increase in γ-glutamyl transpeptidase (GGT) levels [3], which is related to ABCB4 gene mutations. Liver ultrasound is crucial for diagnosing LPAC syndrome, often showing signs of micro calculi in the liver, manifested as comet-tail-like, micro-spots, or bile sludge-like substances in the intrahepatic bile ducts. Since only one-third of LPAC syndrome patients will find gallbladder stones, normal ultrasound examinations cannot rule out this diagnosis. Approximately 5-10% of LPAC patients may have true intrahepatic gallstones, with or without bile duct dilation [3]. In general, micro calculi are normal for LPAC syndrome. In most cases, MRCP does not show micro calculi, and it is not a necessary examination. However, if intrahepatic stones or bile duct dilation are found during ultrasound examination, MRCP is very useful for evaluating the impact of the stones on the bile ducts and liver parenchyma. Not all patients' MRCP examinations can show gallstones, especially when the stone diameter is less than 5 millimetres. A study of 125 LPAC patients showed that all patients were screened based on the available MRCP results, and 49% of the patients had biliary abnormalities, mainly intrahepatic stones (93%) and bile duct dilation (38%) [17]. These morphological abnormalities are more common in patients with pathogenic variants of the ABCB4 gene. In this study, two patients had bile duct dilation (40%), similar to the literature reports [17]. The liver pathological features of LPAC are similar to those of other diseases related to ABCB4 gene mutations. The typical pathological feature of PFIC3 is portal fibrosis and bile duct hyperplasia, with varying degrees of severity of fibrosis, mixed inflammatory infiltration, and small interlobular bile ducts visible in most lobular areas. MDR3 protein immunohistochemical staining can show the expression of this protein in liver tissue [18]. All 5 patients in this study underwent liver tissue pathology examination, and 4 cases (80%) showed small bile duct hyperplasia, 3 cases (60%) suggested liver cirrhosis, and the other 2 cases suggested liver fibrosis. The liver pathology of this study conformed to the characteristics of PFIC3, and the clinical diagnosis was consistent with LPAC.

The diagnosis of LPAC should meet at least two of the following three main diagnostic criteria [1]: (1) Cholangial symptoms appear before the age of 40. (2) Cholangial symptoms persist after cholecystectomy. (3) Ultrasound examination indicates intrahepatic (micro) stones. Secondary diagnostic criteria: Having a family history of gallstone disease in young people (under 40 years old) or an individual or family history of ICP is helpful for diagnosis [3]. Therefore, if only one main LPAC diagnostic criterion and two secondary criteria are found, the diagnosis can be confirmed. However, the clinical manifestations of LPAC are usually not typical. In young patients with gallstones, approximately 30%-50% of patients have ABCB4 mutations, and genetic testing is the gold standard. So far, there is no literature reporting the incidence of LPAC in patients with ABCB4 mutations. However, in the past 10 years of 25 patients with ABCB4 mutations in our center, LPAC accounted for 20%. The sample size needs to be expanded to determine its incidence. If a younger patient with gallstones is encountered in clinical practice, excluding other risk factors causing gallstones, combined with elevated GGT in liver function, genetic testing can be considered for early diagnosis of the disease and UDCA treatment. It may be possible to avoid subsequent cholecystectomy surgery. In this study, all 5 patients had gallbladder or common bile duct stones and underwent cholecystectomy very early. Four patients were diagnosed with this disease many years later due to abnormal liver function or liver cirrhosis and the discovery of ABCB4 gene mutations. However, the exploration of ABCB4 gene mutations is of great significance in clinical research because genetic testing is not a routine examination method in clinical practice, so it is easy to diagnose as regular gallstone disease. However, the difference between LPAC and conventional gallstone disease lies in that there are intermittent abdominal discomfort or repeated cholangial symptoms after cholecystectomy. The clinical characteristics and severity of LPAC may be related to the ABCB4 mutation status. Different mutation types may lead to different clinical symptoms. In this study, patients with deletion mutations have more severe conditions. The complications of LPAC are similar to those of common gallstone complications, including common bile duct obstruction, acute bacterial cholangitis, and acute biliary pancreatitis. The incidence of acute cholangitis in LPAC syndrome (24%) is higher than that of typical gallstone disease (7%). In severe cases, there is also a risk of cholangiocarcinoma. A series study of 308 patients with LPAC syndrome in a French multi-centre study reported 5 cases of intrahepatic cholangiocarcinoma [3]. Although such cases are relatively rare, they highlight the association between ABCB4 gene mutations and the risk of liver and biliary cancer [19]. In this study, one patient progressed to liver cancer and is currently receiving conservative treatment due to the large tumour size.

The treatment of LPAC aims to control biliary symptoms. Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic bile

acid initially used for dissolving cholesterol stones due to its low toxicity [20] and has gradually been applied in the management of cholestatic liver diseases [21, 22]. Recent studies have reported that UDCA stimulates the secretion of bile acids and phospholipids by upregulating the expression of ABCB4, an apical membrane transporter in hepatocytes [23]. Increased phospholipid concentration in bile enhances cholesterol solubility, ultimately leading to dissolution of cholesterol crystals and stones [24, 25]. UDCA also strengthens the innate immune system within the biliary tract, suppresses biliary inflammation, and prevents phospholipid degradation [26]. Furthermore, UDCA inhibits bile acid-induced apoptosis by stabilizing mitochondria and hepatocyte membranes, while enhancing the liver's defines against oxidative stress [27]. In animal models using ABCB4 gene-knockout mice, UDCA treatment has been shown to reduce liver injury and intrahepatic stone formation [28]. Therefore, UDCA has been successfully used in patients with phenotypes associated with ABCB4 gene mutations, such as PFIC3, ICP, and DILI [29]. PFIC3 is linked to homozygous or compound heterozygous ABCB4 mutations, resulting in significantly reduced phospholipid levels in bile; treatment with 20–30 mg/kg/day of UDCA improves liver function and delays disease progression in some patients [30]. The European Association for the Study of the Liver (EASL) recommends UDCA therapy for LPAC patients [6]. Case series reports indicate that UDCA can dissolve intrahepatic stones, improve dilated intrahepatic bile ducts and chronic liver disease, and reduce episodes of biliary pain. Early trials evaluating UDCA for post-cholecystectomy pain demonstrated that it reduces biliary pain episodes and improves quality of life [31]. Milder forms of LPAC typically follow a benign clinical course [32]. In this study, all five patients received long-term UDCA treatment: two had mild disease with stable conditions, while the other three, who had cirrhosis, showed stable liver parameters but exhibited a gradual progression of their condition.

Although UDCA is effective for most LPAC patients, there are still some patients who do not respond adequately to UDCA. For these patients, the FXR agonist Obet cholic acid (OCA) provides a new treatment option. FXR is a key transcription factor that regulates the expression of the ABCB4 gene. Activating FXR can upregulate the transcription of the ABCB4 gene, thereby indirectly promoting the expression of MDR3 protein and bile lipid secretion. A small sample retrospective study involving 5 LPAC patients who failed UDCA treatment initially showed that after OCA treatment, the symptoms of 4 patients improved. Although the imaging signs of stones did not completely disappear in most patients after treatment, the effective control of symptoms is of great significance for improving the quality of life of patients. It should be noted that the evidence for OCA as a second-line treatment option for LPAC is still limited, and its exact efficacy and long-term safety need to be verified by larger-scale, prospective, randomized controlled studies. Ushitinib is a hydrophilic bile acid and MDR3 inducer that can promote the entry of phospholipid substances into bile for secretion and protect the bile duct epithelial cells from the detergent toxicity of endogenous bile acids. Therefore, this drug is the preferred therapy for treating extrahepatic cholangiocarcinoma syndrome [33]. The second-line treatment for LPAC can also use ezetimibe, which can reduce the cholesterol concentration in bile and bile stones in animal models. MDR3 inducers, such as fatty acid derivatives or obetinib, are used for treatment. For symptomatic bile duct stones, endoscopic retrograde cholangiopancreatography (ERCP) removal surgery may be necessary. In a retrospective study on patients with LPAC syndrome, 30% of the patients required ERCP treatment, but this situation usually occurred before the diagnosis of LPAC and before the start of UDCA treatment [34]. Most of the stones caused by LPAC are of the cholesterol type, are light yellow in colour and soft in texture. The results of ERCP are good, with a success rate of over 80%. For patients with LPAC syndrome, it is advisable to avoid cholecystectomy as much as possible, as it cannot prevent the recurrence of biliary events, and these events are mostly related to intrahepatic stones. Only in cases of acute cholecystitis should cholecystectomy be performed to reduce the risk of complications. However, before diagnosis, nearly 80% of patients will undergo cholecystectomy. In cases of severe biliary obstruction in the intrahepatic bile ducts accompanied by symptoms or complications and with no response to UDCA treatment, partial liver resection can be considered. Liver transplantation is not necessary in most cases, and it is only applied to a very small number of cases of diffuse intrahepatic bile duct stone obstruction with recurrent life-threatening cholangitis or advanced biliary cirrhosis.

LPAC syndrome is a genetic disorder of bile phospholipid deficiency caused by mutations in the ABCB4 gene, representing a unique and important subtype in the field of gallstone diseases. Currently, there are still many unanswered questions regarding this disease. LPAC patients are mostly found in young adults, caused by a single gene mutation of ABCB4, and gallbladder stones usually appear after adulthood. If abnormal transaminase levels and elevated GGT are detected in young adults with gallbladder stones, this disease should be considered. Early genetic testing for diagnosis should be performed, and UDCA treatment can improve prognosis and possibly prevent gallbladder removal. The effectiveness and safety of the second-line drug OCA urgently need to be confirmed by large-sample studies; the true extent of the tumour risk also needs to be systematically evaluated based on large-scale cohorts. In China, there are very few clinical reports on LPAC syndrome. On the one hand, this suggests that there may be missed diagnoses; on the other hand, it also indicates that the genetic heterogeneity of this disease among different ethnic groups still needs to be further explored.

6. Conflict of Interest Statement

The corresponding authors declare that they have no conflict of interest relevant to the present study.

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