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Review Article

Approach and management considerations in low phospholipid associated cholelithiasis (LPAC) syndrome

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ABSTRACT

Low phospholipid associated cholelithiasis (LPAC) syndrome, first described in 2001, could be the causality in a significant number of young patients with cholelithiasis, who have a recurrence of symptoms despite cholecystectomy. A mutation of the ABCB4/MDR3 gene, causes a disruption in the translocation of phosphatidylcholine, resulting in bile acid mediated biliary tract injury. The ABCB4 gene is also implicated in other diseases such as progressive familial intrahepatic cholestasis type 3, which is greater in severity and tools like genotyping can aid the physician in prognostication, as well as determining the response to medical therapy. A few symptomatic patients develop features of biliary obstruction due to intrahepatic calculi, and they require interventions-which may be endoscopic or surgical in nature. Although a majority of patients with LPAC syndrome respond well to ursodeoxycholic acid (UDCA) therapy, close monitoring is warranted to keep a check on disease progression.

Keywords: Cholelithiasis, Gallstones, intrahepatic calculi, LPAC, UDCA

INTRODUCTION

Recurrent cholelithiasis in young individuals often poses a management conundrum for most physicians. The problem in itself carries significant morbidity, with many patients experiencing episodes of cholecystitis, cholangitis, pancreatitis and rarely, intrahepatic calculi. Low phospholipid associated cholelithiasis (LPAC, OMIM 171060), first described in 2001, is a condition characterized by biliary phospholipid deficiency and cholesterol supersaturation could be responsible for a significant number of obscure cases.[1]

Diagnostic criteria have been formulated which have significantly increased the identification rate of this condition (Table 1).

The exact prevalence of LPAC remains unknown, but some studies have considered it to be as high as 5% of all symptomatic gall stone disease.[2,3] The disease is more common in young adults, the usual age at the onset of the symptoms is typically lower than 40 years (most commonly during the second and third decade of life). Females are three times more likely to be affected than males.[3]

Table 1: Clinical diagnostic criteria for LPAC syndrome (at least three of the following).

Clinical diagnostic criteria for LPAC syndrome
Age of onset of symptoms below 40 years
Presence of intrahepatic hyperechoic foci with a topography compatible with lipid deposits along the luminal surface of the intrahepatic biliary tree +/- intrahepatic sludge or microlithiasis.
Recurrence of biliary symptoms despite cholecystectomy
Familial history of cholelithiasis in first-degree relatives Association with cholangitis, cholecystitis or acute pancreatitis.

REVIEW OF LITERATURE

Pathophysiology

Phospholipids such as phosphatidylcholine are the major solvents and transporters of cholesterol and also demonstrate a protective effect against bile acid induced biliary mucosal injury.[4,5] Human multidrug resistance 3 (MDR3) is mainly expressed on the canalicular membrane of hepatocytes and plays an important role in the protection of the liver through translocation of phosphatidylcholine from the inner leaflet to the outer leaflet of the canalicular membrane and this floppase activity enables phosphatidylcholine to be extracted into the canalicular lumen by bile salts.[6,7]

Unchaperoned bile acids are encountered in patients with MDR3 deficiency, which is thought to play an important role in the development of cholangitis, biliary epithelial damage, bile ductular proliferation, and progressive portal fibrosis. Individuals with an increased cholesterol saturation index are predisposed to cholesterol gallstones.[8] The absence of biliary phospholipids may increase the lithogenicity of bile due to the destabilization of micelles and promote the crystallization of cholesterol. Chronic biliary inflammation may increase cholangiocyte turnover, leading to the growth of altered cholangiocytes and increased susceptibility to cholangiocarcinoma.

Genetic mutations in LPAC syndrome

The ATP-binding cassette, subfamily B, member 4 gene (ABCB4), a 1279 amino acid transmembrane protein with 27 coding exons and spanning approximately 74 kb, codes for MDR3 and is located on chromosome 7q21.1.[9] ABCB4 protein is mainly expressed in the liver, although low levels of ABCB4 mRNA expression are found in the adrenal gland, muscle, tonsil, spleen, placenta, testis, and ileum.

Two frequently encountered ABCB4 missense mutations detected in patients with the LPAC syndrome are Glu528Asp and Thr175Ala; other mutations have also been reported in literature (Table 2).[10] Partial or complete heterozygous ABCB4 deletions occur in approximately 7% of the patients with LPAC.[11]

Table 2: Frequently encountered ABCB4 mutations associated with LPAC syndrome.

Frequently encountered abcb4 mutations associated with LPAC syndrome	
GLU528ASP	SER320PHE
THR175ALA	ALA934THR
PHE165ILE	1006-1016INST
1327INSA	1006-1016DELT
PRO1161SER	S320F

Affected patients with heterozygous mutations exhibit one base pair-insertion or deletion, non-sense mutations or missense mutations resulting in a frameshift likely causing premature messenger RNA termination, single-nucleotide substitutions and a loss of protein function, while affected patients with homozygous mutations demonstrate only missense mutations. Most mutations are localized close to nucleotide binding domain 1 (NBD1), in the central part of the molecule or in adjacent transmembrane domains and intracellular loops. Approximately 80% of mutations occur in regions encoded by exons 9 to 18.[10]

In addition to the ABCB4 gene, one article reported the presence of a mutation in the ABCB11 gene in LPAC. The ABCB11 gene encodes the bile salt export pump (BSEP), which transports bile salts across the canalicular membrane of the hepatocyte, the limiting step in bile secretion. Although mutations in BSEP are linked to progressive familial intrahepatic cholestasis type 2(PFIC2), benign recurrent intrahepatic cholestasis type 2 (BRIC2), intrahepatic cholestasis of pregnancy (ICP), and drug-induced liver injury (DILI). Of note, in contrast to most MDR3-related diseases, normal GGT activity is often seen in BSEP mutation associated disease, due to low levels of biliary bile salts and consequently less cholangiocyte damage.

Investigation of the genotype-phenotype relationships in LPAC patients, reveals that a few nonsense mutations are associated with an earlier onset of symptoms, while biliary complications or the frequency and severity of intrahepatic cholestasis of pregnancy were not related with the mutant type.

Spectrum of ABCB4 mutations

In addition to LPAC syndrome, ABCB4 mutations have also been linked to conditions such ICP, transient neonatal cholestasis, PFIC3, and adult idiopathic biliary fibrosis or cirrhosis.[12-15]

PFIC3 is an autosomal recessive condition and patients mostly have homozygous or compound heterozygous missense, non-sense, micro frameshift insertions or

deletion mutations of the ABCB4 gene. These patients have no or very low levels of canalicular ABCB4 protein and low biliary phospholipid levels. The course of illness is far more severe than in LPAC, with onset of symptoms at a very young age. The presence of progressive and severe chronic cholestasis, along with high serum gamma glutamyl transferase activity is characteristic of this condition. Features of portal fibrosis and inflammation with prominent biliary ductal proliferation in an early stage is usually seen on hepatic histology.[16] Portal hypertension and cirrhosis are frequently encountered putting the patients at risk for gastrointestinal bleeding, and roughly half of them end up being candidates for liver transplantation. An interesting point is the utility of UDCA in almost 50% of the patients-this may be explained by the presence of partial ABCB4 defects (missense or deletions) and hence genotyping could help identify patients who would benefit from UDCA therapy.[13]

Loss of function ABCB4 mutations can present a large spectrum of cholestasis phenotypes. However, in a significant proportion of patients, no ABCB4 mutations are detected. The lack of discovering ABCB4 mutations in probable cases might be attributed to phenotyping errors, genetic heterogeneity, and inadequacy of genetic screening methods.

DISCUSSION

Clinical description

LPAC typically has an onset of symptoms in young adults during the second and third decades of life. Patients may present with recurrent cholelithiasis, biliary microlithiasis, cholecystitis, cholangitis, pancreatitis and intrahepatic calculi. Many patients undergo cholecystectomy, but almost half of them get re-hospitalized due to recurrence of symptoms. Many patients also report a history of cholesterol gallstones in their first-degree relatives.[10]

The absence of detectable gallstones in a subset of patients may suggest that biliary symptoms experienced by them are probably caused by cholesterol crystal deposits and biliary ductal inflammation. Most patients with LPAC syndrome usually tend to have a disease course with less severity compared to PFIC3 patients, but in a small subset, the disease may have severe consequences such as development of biliary cirrhosis or intrahepatic non cystic biliary duct dilatations.[10]

The relatively higher incidence of LPAC syndrome observed after middle adolescence and that of young females heterozygous for pathogenic mutations in ABCB4 developing contraceptive induced cholestasis (CIC) or manifesting previously asymptomatic gallstones during administration of combined oral contraceptives are likely due to changes in biliary lipid composition during the second decade of life. Children rarely develop gallstones, but calculi are frequent in adults; this difference may be attributed to the low concentrations of cholesterol in the bile of children. Children have reduced biliary cholesterol:bile salt excretion ratios. Therefore, even at low rates of phospholipid secretion caused by incomplete MDR3 deficiency, bile is not saturated with cholesterol.

Young adults have an increase in the biliary cholesterol saturation index, together with the decreased biliary secretion rate of phosphatidylcholine in carriers of mutations in ABCB4, shifts the cholesterol-solubility equilibrium to the borderline. Even small quanta of exogenous hormones contained in contraceptives or other hormonally active drugs, which inhibit bile salt secretion and further reduce the secretion of phospholipids into bile proportionally to bile salt flow, can precipitate cholestasis and promote cholesterol crystallization from supersaturated bile, with intrahepatic sludge and gallstone formation. Thus, the clinical criteria for LPAC caused due to ABCB4 mutations, may not be applicable to children with idiopathic gallstones, as even young carriers of the mutations might not manifest LPAC due to sexual immaturity.

Patient evaluation

Investigations which should be considered in a patient with LPAC syndrome are described below:

Hematological investigations

Complete blood count: Elevated total counts, neutrophilia are seen in patients with cholangitis or cholecystitis.

Liver function tests: Elevated levels of serum total bilirubin (STB) with mild to moderate elevation of transaminase levels, gamma glutamyl transferase, alkaline phosphatase and a mild derangement of Prothrombin time may be observed. Elevation of serum amylase and lipase in case of pancreatitis.

Lipid profile: Hyperlipidemia is usually noted.

Liver bile analysis

Collection of hepatic bile can be done after selective cannulation of the common bile duct during ERCP and compared with reference values (Table 3). Analysis of hepatic bile in LPAC patients will show a low phospholipid concentration, high biliary cholesterol, a high cholesterol saturation index, the presence of numerous cholesterol monohydrate crystals and a high cholesterol-to-phospholipid ratio.[17]

The relative proportion of lipids in hepatic bile is known as the cholesterol saturation index (CSI) or lithogenic index (LI) and is the major indicator determining whether bile is over-saturated with cholesterol (CSI>1.0) or within desirable levels (CSI<1.0). CSI>1.0 is a prerequisite for

cholesterol gallstone formation. CSI is calculated by dividing the cholesterol concentration by the maximum cholesterol solubility according to Carey and Small, and corrected for the total lipid content of each individual bile.[18,19]

Table 3: Normal parameters of hepatic and gall bladder bile.

Parameter	Hepatic bile	Gall bladder bile
pH	7.5	6.0
Bile Acids (g/L)	3-45	32
Total Fatty Acids (g/L)	2.7	24
Bilirubin (g/L)	1-2	3
Phospholipids (g/L)	1.4-8.1	34
Cholesterol (g/L)	1-3.2	6.3
Proteins (g/L)	2-20	4.5
Total Phosphorous (g/L)	0.15	1.4
Sodium (mM)	141-165	220
Potassium (mM)	2.7-6.7	14
Calcium (mM)	1.2-3.2	15
Chloride (mM)	77-117	31
Bicarbonate (mM)	12-55	19

Genetic analysis

Genomic DNA analysis of peripheral white blood cells using polymerase chain reaction (PCR) technique reveals mutations of the ABCB4 gene. Multiplex ligation dependent probe amplification (MLPA) is a sensitive, rapid, and cost-effective approach that seems particularly adapted to routine diagnosis in molecular genetics. In case of ABCB4 negative sequencing in patients with suggestive phenotype, a molecular algorithm tailored to ABCB4 routine analysis that includes ABCB4 gene dosage by MLPA can help in identification. MLPA allows a fast and inexpensive first-line screening for both the partial and complete ABCB4 deletions, complementary to a high-resolution technique such as array-comparative genomic hybridization- that can be used to characterize larger deletions. Real-time PCR-based gene dosage is useful for deletion's confirmation

Imaging studies

A wide spectrum of biliary abnormalities might be encountered, which are non specific, and may include choledocholithisis, dilatation of intrahepatic biliary radicles, intrahepatic calculi etc. Among these, intrahepatic calculi, which are defined as those gallstones occurring in any of the intrahepatic bile ducts proximal to the biliary confluence irrespective of the presence of calculi in the extrahepatic bile duct, are the most peculiar finding in LPAC syndrome (Figure 1a, 1b).[10] These calculi usually tend to involve one single liver segment or lobe, and occur more commonly in the left biliary system.[20]

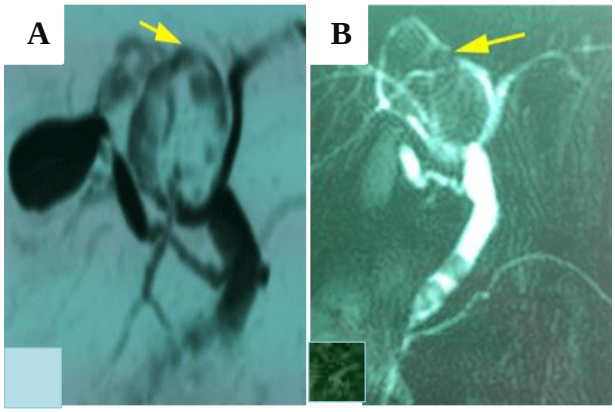

Figure 1: MRCP Images. A) MRCP Image showing Intrahepatic calculi at the biliary confluence in a patient with LPAC syndrome. B) MRCP image showing intrahepatic calculi at the biliary confluence with distal CBD calculi and normal pancreatic duct.

Abdominal Ultrasonogram (USG)

USG is an accurate initial investigation that aids in detecting intrahepatic stones. They appear as heterogeneous echoic foci centered on the intrahepatic ducts, or as "comet-tail artifacts".[21] Localisation of the calculi, indeed may present a challenge to the sonologist, and may warrant an advanced imaging modality.

Endoscopic ultrasound (EUS)

It may have a greater utility in detection of intrahepatic calculi in the left biliary system than those in the right.

Magnetic resonance cholangiopancreatography (MRCP)

MRCP is a non-invasive advanced imaging technique that has shown equivalency to ERCP in choledocholithiasis diagnosis and superior to ERCP in intrahepatic lithiasis diagnosis.[22] The presence of round or oval shape endoluminal signal voids in the bile ducts on heavily T2-weighted sequences may be noted. Calculi may have high signal on T1-weighted sequences or strong hypointensities on T1-weighted acquisitions.[21]

Additional evaluation by USG and MRI should be recommended because MR is not able to detect very small stones, while USG may be difficult in case of massive intraluminal stones. Hepatic atrophy may also be noted.[23]

Contrast enhanced computerised tomography (CECT)

The sensitivity of CECT is limited in case of LPAC syndrome due to the presence of cholesterol calculi instead of pigment calculi (Figure 2).

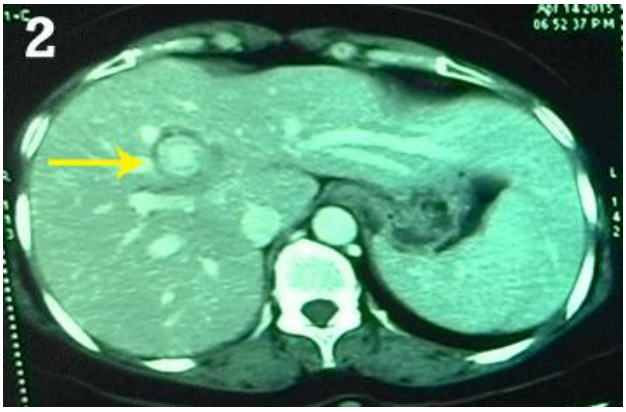

Figure 2: CECT abdomen image showing the presence of intrahepatic calculus.

Cholangioscopy

Percutaneous transhepatic cholangioscopy (PTHC) and direct peroral cholangioscopy (DPOC) are methods which allow direct visualization of the bile ducts in addition to providing a route for therapeutic interventions. The utility of DPOC however, may be limited by difficult access owing to the sharp angulations in biliary anatomy and reduced intrahepatic ductal size making manoeuvrability difficult.[24]

Management

The main objectives in the management of this disease are to extract all intra- and extrahepatic stones, and to remove any bile duct stenosis, affected bile duct drainage areas and all atrophic segments

Surgical management

The left liver lobe is often the most frequent location of hepatolithiasis.[20] The acute angle taken by the left hepatic duct when it reaches the confluence resulting in biliary stasis, especially in the background of biliary stenosis. Some studies have shown a higher frequency of right side involvement, especially in the posterior segments of post-cholecystectomy patients.[25] This may be due to an anatomical variant where the posterior segment artery comes from the common hepatic artery or due to a branch passing through the gallbladder fossa, which can be injured during cholecystectomy, resulting in ischaemia of the local bile ducts.[26] The surgical approach to cases of intrahepatic calculi are highly individualized. In the past, many patients were subjected to a choledochotomy or choledochoduodenostomy. Due to the expected need for long term access to the intrahepatic biliary ducts, procedures such as hepaticocutaneous jejunostomy with subcutaneous access loop, were favoured subsequently.[20]

In case of large calculi (especially in the left lobe), hepatic atrophy, abscesses, suspected cholangiocarcinoma or failure of other therapeutic modes, surgical resection may be considered appropriate. Procedures such as lobectomy, partial hepatectomy, segmental resection etc. are routinely performed by hepatobiliary surgeons in indicated cases. Considering the most frequent loci of intrahepatic calculi, left lateral sectionectomy is the most frequently performed procedure followed by right posterior sectionectomy and left hepatectomy.[25]

In patients with symptomatic gallstones, cholecystectomy is indicated. The presence of sludge alone in the gall bladder should not bias the surgeon.

Laser lithotripsy (LL)

Laser light pulsed at a specific wavelength causes wave mediated fragmentation of calculi. LL is ideally performed under direct cholangioscopic visualization in order to avoid biliary injury and may achieve ductal clearance rates ranging from 64% upto 97% in patients.[27,28] In the majority of cases, a single session would be sufficient, and LL is being preferred over electrohydraulic lithotripsy (EHL) in many centres. The Spyglass direct visualization system (Boston Scientific Corp., Natick, Massachusetts) offers the advantages of single operator manoeuvring, dedicated irrigation and multi-directional steering, but has lower resolution image quality compared to newer video-cholangioscopes.[29]

Genetic counselling

ABCB4 genotyping should be used to confirm the diagnosis of LPAC syndrome in young adults. Mutation analysis may also be beneficial to identify individuals who will benefit from UDCA therapy.[23]

Medical treatment

UDCA

In all cases with confirmed ABCB4 mutations, long term prophylactic or curative therapy with UDCA (13-20 mg/kg/day) should be initiated. UDCA protects the hepatocytes from bile acid induced apoptosis, reduces concentration of hydrophobic bile acids in the cholangiocytes, promotes insertion of transporter molecules into the canalicular membrane of the hepatocytes and also reduces the bile acid cytotoxicity of bile.[30] UDCA decreases the degree of cholangiocellular injury, portal inflammation, and ductular proliferation and retards the progression to cirrhosis. A few studies have demonstrated significant decreases in bile salt-to phospholipid ratios and cholesterol-to-phospholipid ratios with UDCA dosage of 600 mg/day.[23]

Statins

Statins decrease cholesterol synthesis through competitive inhibition of the rate-limiting enzyme (HMG-CoA reductase) thereby reducing the amount of cholesterol available for secretion into plasma and/or bile.

Whereas, a reduction of plasma cholesterol secretion often results in a reduction in plasma LDL, a reduction in the secretion of cholesterol in bile likely results in a more favourable biliary lipid profile that may prevent cholesterol calculi development/growth or even their dissolution. Patients with cholesterol saturated bile are more likely to show a decrease in CSI with statin treatment.[31] Studies have shown a significant decrease in hepatic bile CSI in the range of 27-47%, and upto 22% reduction in the bile acid hydrophobicity index.[32] Although there is no evidence to support the use of statins in primary or secondary prevention for cholesterol gallstones, its use as an alternative to surgery or in patients at high risk for cholesterol calculi, such as in some families, cannot be underestimated, particularly in combination with UDCA, which seems to have a synergistic effect. Statins should be preferred to fibrates which increase the lithogenic tendency of bile.[32]

Newer drugs

Constitutive androstane receptor (CAR) plays an important role in maintaining the homeostasis of cholesterol and triglyceride levels and its activation may represent a new approach for treating hepatolithiasis in LPAC syndrome.[33]

Ezetimibe is a highly selective intestinal cholesterol absorption inhibitor by suppressing the uptake of dietary and biliary cholesterol across the brush border membrane of the enterocyte through the NPC1L1 pathway. In some studies, 30 days of treatment with ezetimibe at 20mg/day significantly reduced cholesterol concentrations and CSI values of bile in patients with gallstones.[34]

Liver transplantation

Patients with end-stage liver disease may be candidates for liver transplantation

Clinical course and outcome

Although LPAC has a progressive course, with recurrence of symptoms in-spite of surgical intervention clinical improvement is evidenced after initiation of UDCA therapy. Unlike PFIC3, the majority of patients with LPAC syndrome do not develop recurrence or end-stage liver disease under medical treatment.

CONCLUSION

In young adults with recurrent episodes of cholelithiasis and intrahepatic calculi, LPAC needs to be considered as a differential diagnosis and it is no longer prudent to ignore it as an orphan disease. Although LPAC is associated with ABCB4 mutations, the presence of a wide variety of ABCB4 related genetic mutations renders the identification of genotype-phenotype correlations difficult. The clinical criteria applicable to young adults with LPAC who have ABCB4 mutations, might not be applicable to young children who may be carriers of the genetic mutation, but might remain asymptomatic due to the difference in their bile composition and sexual immaturity. Gene dosage technologies have allowed the identification of ABCB4 deletions in approximately 7% of patients with LPAC syndrome. An early diagnosis of this biliary disease would be beneficial because it would allow physicians to initiate early therapy with UDCA and thereby prevent biliary complications.

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