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LPAC syndrome: case report and literature review

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ABSTRACT

LPAC syndrome (Low Phospholipid-Associated Cholelithiasis) is a particular form of intrahepatic cholestasis, occurring in young adults. It is characterized by at least two of the following criteria: (1) onset of symptoms before age 40; (2) presence on ultrasound of echogenic foci or intrahepatic microlithiasis; (3) recurrence of symptoms after cholecystectomy. It is secondary to a deficiency of the phospholipid transporter the MDR3 protein. The majority of cases are under diagnosed. In our observation, we report the case of a patient with LPAC syndrome, diagnosed 20 years after the onset of symptoms. This is a 51-year-old patient with chronic intermittent hepatic colic since the age of 30, a cholecystectomy for acute cholecystitis in 1999. At the age of 32 years the patient reports the recurrence of the symptomatology with the ultrasound lithiasis of the common bile duct, so the patient has benefited from a surgical extraction of the lithiasis of the common bile duct.The evolution was marked by persistent symptomatology, repeated episodes of cholangitis, iterative para-clinical examinations and demanding hospitalizations. Face to this clinical presentation and a negative etiological assessment , a genetic study for mutational research of hepatobiliary transporter genes has been proposed. This objectified the presence of the false sense variant of the ABCB4 / MDR 3 gene in the heterozygous state. The diagnosis of LPAC syndrome is retained and the patient is put under AUDC. The evolution is marked by a clinical improvement

Keywords *:LPAC, intrahepatic cholestasis, ABCB4/MDR3 gene*

INTRODUCTION

Low Phospholipid-Associated Cholelithiasis (LPAC) is a particular form of intrahepatic cholestasis of the young adult. This syndrome can be retained in the presence of two of the following criteria: the occurrence of the first symptoms before the age of 40; the presence of echogenic foci or intrahepatic microlithiasis on ultrasound; recurrence of symptoms after cholecystectomy (1). It is due to a deficiency of the phospholipid transporter MDR3, encoded by the ABCB4 gene. Although LPAC syndrome has a simple treatment based on ursodesoxycholic acid (UDCA), the majority of cases are not diagnosed. (1,2)

We report through this observation the case of a patient with LPAC syndrome, diagnosed after 20 years of clinical suffering.

MATERIALS AND METHOD

Observation:

A 51-year-old patient with intermittent hepatic colic since the age of 30, with cholecystectomy for acute cholecystitis in 1999 with recurrence of painful seizures after 2 years, ultrasound examination showed the presence of lithiasis in the common bile duct evoking a residual lithiasis of the common bile duct for which it has benefited from a surgical extraction. The evolution was marked by the persistence of hepatic colic and the appearance of an intermittent conjunctival sub-jaundice. The initial etiological assessment did not show any anomaly.

In May 2015, the patient presented an acute cholangitis on choledocholithiasis. The imaging had objectified a dilation of the intrahepatic bile ducts, the right posterolateral sector seat of multiple lithiases, these lithiases also interested the right hepatic duct and convergence and part of the common hepatic duct. The supra-pancreatic bile duct was dilated to 9 mm with a heterogeneous content made of a multitude of lithiases. Thus, the patient benefited from retrograde endoscopic cholangiography, which allowed the extraction of 11 stones.

In front of the early age of onset of symptomatology, the recurrence of painful crises after cholecystectomy and the results of imaging, a genetic study for mutational research of hepatobiliary transporter genes has been proposed. This objectified the presence of the false sense variant of the ABCB4 / MDR 3 gene in the heterozygous state. The diagnosis of LPAC syndrome was therefore retained and the patient was put under UDCA with slight decrease in abdominal pain

Following the recurrence of hepatic colic, the patient had opted for a US diet for cleaning the liver and gallbladder from the book by Andreas MORITZ. This diet is based on water, apple juice, fresh grapefruit juice, olive oil and Epsom salts. From the 7th day of the cure, the patient reports the notion of disappearance of hepatic colic and salt emission mixed with gallstones of different sizes and colors. This phenomenon of easy and painless removal of gallstones pushed our patient continued and repeated this cure several times.

Six months later, the patient had a new episode of cholangitis for which she had been hospitalized for two weeks, and the imaging revealed dilation of the intrahepatic bile ducts and of common bile duct with macrolithiases. Thus a complement by retrograde cholangiograpphy was carried out in urgency allowing the extraction of 21 stones.

Our conduct is to continue the UDCA treatment and to stop the liver and gallbladder cleansing diet in the face of the rapid process of stone production and the risk of recurrent angiocholitis in a high-risk patient. Our patient reports a clear clinical improvement.

RESULTS AND DISCUSSION

We report an observation of LPAC syndrome or genetic cholesterol lithiasis. This syndrome is a rare genetic disorder. This is a very particular form of cholelithiasis described for the first time in 2001 by the team at Saint-Antoine Hospital. (3)

Most cases of LPAC syndrome are under diagnosed. This lack of diagnosis is mainly explained by

the lack of knowledge of the clinical context and radiological signs. This delay in diagnosis was confirmed by the LPANGH study, which showed an average delay of 8 years between the first symptoms and the diagnosis of LPAC syndrome. (4)

Its prevalence is unknown, observed in a small subgroup of patients with symptomatic stones. (5,2)

The average age of onset of symptoms is 26 to 32 years, in 10% of cases the first symptoms appear after 40 years and exceptionally the symptoms appear after 50 years. (6)

This syndrome is characterized by a female predominance with a sex ratio of 1/2, 3 and 1/5. This predominance is explained by the aggravating role of estrogen, responsible for the inhibition of phospholipid secretion in bile. The role of estrogen explains the occurrence of symptoms 10 years earlier in women, intrahepatic cholestasis caused by oral contraceptive use in young women with ABCB4 mutation and the frequent onset of symptoms in late pregnancy. (6,7)

The excretion of phospholipids in the bile at the canalicular pole of the hepatocytes is provided by the phospholipid transporter (MDR3 protein: multidrug resistance 3, encoded by the ABCB4 gene). The ABCB4 gene is located on chromosome 7q21. Contains 27 coding exons, and spans about 74 kb. In 33-50% of cases of LPAC syndrome, mutations of the ABCB4 gene were logically identified as being responsible for the LPAC syndrome, which is predominantly heterozygous with missense mutation. As a result, when the phospholipid transporter is deficient, the bile acids are transported without phospholipids and will thus form simple micelles that do not have the ability to solubilize cholesterol. This results in the formation and precipitation of micro-crysts and cholesterol stones in the small intrahepatic bile ducts. In addition, bile acids transported without phospholipids have a detergent effect resulting in lesions of the biliary epithelium, proliferation of the bile duct, and potential progressive portal fibrosis. (8,1,9,5,10,11)

the studies of the Saint Antoine team in 2003 were able to report for the first time that the presence of at least two of the following three criteria was strongly associated with the ABCB4 mutation: the onset of symptoms before the age of 40; recurrence of symptoms after cholecystectomy; ultrasonographic evidence of focal hyperechoic abnormalities compatible with cholesterol deposition along the small intrahepatic bile ducts (comet tail aspect and / or intrahepatic lithiasis, other elements may point to a syndrome LPAC including family history of lithiasis before age 40 and / or atypical cholestasis table often liver tests often mildly disturbed (hepatic cytology and moderate elevation of GGT.) Moreover, the same team showed that the clinical characteristics, radiological and bile analysis of patients with LPAC syndrome without ABCB4 mutation were identical to those of mute patients for ABCB4, however, ABCB4 mutations were only found in one-third to one-half of LPAC (7.1, 2.11)

Syndrome LPAC untreated or undiagnosed may be responsible for a repetition of biliary symptoms, a risk of pregnancy cholestasis and prematurity, a very rare chronic cholestasis, secondary biliary cirrhosis and Exceptionally a cholangiocarcinoma. (4,2,12)

It is well known that inactive MDR3 is responsible for the accumulation of altered bile in hepatocytes and cholangiocytes, thus causing microscopic forms of liver damage such as inflammation and fibrosis. Chronic Biliary Inflammation may increase the turnover of cholangiocytes, thereby promoting the growth of altered cholangiocytes and leading to increased susceptibility to cholangiocarcinoma (13,14).

The study by Tougéron suggests a need for prospective follow-up of patients with MDR3 mutations, in order to identify the risk of Cholangiocarcinoma. It would probably be also interesting to look for

an MDR3 mutation in young patients with cholangiocarcinoma, especially if there is a family history of cholangiocarcinoma or biliary disease. (15)

Prevention of the onset and recurrence of lithiasis is a major therapeutic problem in patients with LPAC. The medical treatment described for its clinical and radiological efficacy is the UDCa. This long-term treatment is essential to prevent recurrence of biliary symptoms or serious complications. It must also be maintained during and after pregnancy (except for the first trimester). For surgical treatment, Cholecystectomy is not recommended. does not prevent recurrence of symptoms, it can be justified if there is a symptomatic vesicular lithiasis. Endoscopic drainage or hepatic resection in case of symptomatic biliary galling. In the particular form of LPAC syndrome with intrahepatic biliary duct dilation around macro-calculi, recourse to resection of the affected segment or lobe may be justified if the patient presents recurrent cholangitis despite treatment with UDCA. (2.16)

In LPAC, monitoring is clinical every 6 months by liver tests and abdominal ultrasound to follow the progressive disappearance of bile crystals. A family screening by ultrasound and genotyping may be proposed during the consultation to parents over the age of 18 years. (2)

CONCLUSION

The LPAC syndrome is a rare but not exceptional disease, we must always think of it in front of evocative elements such as the young age of the patients, the post-cholecystectomy recurrence, the cholestasis of pregnancy and the family antecedents. Radiologists must be well educated and sensitized so as not to miss the evocative signs of LPAC.

In the near future, genotyping ABCB4 should be used more and more to confirm the diagnosis of LPAC syndrome in young adults who have a cholelithiasis symptom and allow family screening. In prolonged treatment, the UDCA could be initiated early to prevent the onset or recurrence of this syndrome and its serious complications.

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