CAROLI’S DISEASE: CASE REPORT WITH BIBLIOGRAPHICAL REVIEW

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Abstract: Objective: To report a clinical case of a young woman with Caroli’s disease, highlighting the best method to establish the diagnosis and perform follow-up. Method: Retrospective qualitative study of a case report. Result and discussion: We report the case of an adolescent with a presumptive diagnosis of Caroli’s disease, as well as the diagnostic approach of the same, associated with a brief bibliographic review on the disease. Final considerations: In view of the rarity of Caroli’s disease, it is essential to report a case like this to emphasize that such a diagnostic hypothesis must be considered in the context of recurrent cholangitis, especially in childhood and young adults. It is also essential to emphasize the importance of magnetic cholangioresonance in the investigation.

Keywords: Carol’s Disease. Magnetic resonance cholangiopancreatography. Bile ducts.

INTRODUCTION

First described in 1958 by the French gastroenterologists Jacques Caroli et al., Caroli’s disease (DC) is a rare congenital malformation (mostly autosomal recessive) characterized by a biliary abnormality consisting of segmental saccular dilations of the bile ducts intrahepatic, and may involve the biliary tract in a focal or multifocal manner. With the bile flow partially blocked, there is a predisposition for the formation of calcium bilirubinate calculi, which may be stored in the saccular dilations or impact the common bile duct, causing cholangitis. This can also occur due to the simple delay in bile flow, responsible for recurrent episodes.

Its incidence is approximately 1 in every 1,000,000 individuals and is increasing in prevalence due to the probable advancement of imaging tests, facilitating its diagnosis. DC is part of the group of cystic congenital diseases that were classified by Alonso Lej and Todani in 1977 according to the involvement along the biliary tract, namely: I- Cyst limited to the extrahepatic biliary tract; II- True diverticulum of extrahepatic duct; III- Choledocele or duodenal duplication IV- multiple cysts (a - intra and extrahepatic and b - extrahepatic) and currently considered as group V - Caroli’s disease.

The most accepted theory of its pathogenesis relates it to the anomaly in the development of the ductal plate at different levels of the intrahepatic biliary tree, generating the characteristic malformation. The embryological process of the biliary tree begins with a remodeling plaque. Under normal circumstances, the plaque undergoes epithelial proliferation and cell death until the correct modeling of the bile duct. An interruption or derangement in this process causes the persistence of embryonic bile duct structures in the ductal plate configuration, which may be apparent microscopically or macroscopically. Depending on the stage of reorganization of the malformed plaque, different pathologies can develop - alone or in combination -, varying in degrees of persistent structures of the embryonic bile duct, fibrosis and ductal dilatation.

In DC, liver involvement is limited to the development of cysts and usually presents with abdominal pain in the right upper quadrant, obstructive jaundice, and cholangitis. In Caroli’s syndrome, cystic disease coexists with congenital hepatic fibrosis, which is histologically characterized by mild portal fibrosis and hyperproliferation of interlobular bile ducts within portal areas with preservation of lobular architecture. In this case, the clinical presentation is usually due to liver failure and portal hypertension, with findings such as splenomegaly, ascites, peripheral edema, coagulation disorders and esophageal varices. Both in the disease and in the syndrome, several conditions may...
be associated, such as choledochal cysts, autosomal recessive polycystic kidney disease (DRPAR) or dominant polycystic kidney disease (DRPAR), medullary spongy kidney and medullary cystic disease.8

Taking into account the rarity and possible aggressiveness of this disease, with limited descriptions throughout the world, this study presents a report of Caroli’s Disease, with the aim of increasing the existing knowledge base and helping other health professionals to recognize it as soon as possible. their condition, as well as the importance of outpatient follow-up of patients to avoid adverse outcomes.

**CASE REPORT**

Female patient, 19 years old, referred to the hepatology service from Hospital Santa Casa de Misericórdia de Vitória (HSCMV) for follow-up after cases of cholangitis to be clarified.

In the first consultation, in 2017, she reported two previous episodes of cholangitis in childhood: the first in 2008 (at age 9), requiring hospitalization in a pediatric gastroenterology ward for one month, with no established diagnosis at discharge; and the second in 2014. In both, he presented with a fever of approximately 39ºC, abdominal pain in the right hypochondrium and epigastrium, jaundice and hyporexia. The father denied a past history of biliary tract or liver diseases, recent travel history, tattoos, history of viral hepatitis or use of hepatotoxic substances. On the occasions of the narrated episodes, no triggering factor for cholangitis was identified. He also reported having tested negative for viral hepatitis and had an abdominal ultrasound without any abnormalities described. In 2014, with the repetition of the clinical picture, the hypothesis of Caroli’s Disease (DC) was raised, which remained unproven, and magnetic cholangiography was performed by another service, which was the diagnostic method of choice for DC. Still in 2014, she started prophylactic use of ciprofloxacin associated with sulfamethoxazole and trimethoprim every fortnight, and has been asymptomatic since then. In 2017, nine years after the first manifestation of the disease, magnetic resonance cholangiography was performed.

In HSCMV care, after extensive laboratory evaluation, no hepatocellular lesions, increased canalicular enzymes, reduced kidney and liver function or any other laboratory alteration were found. The possibilities of acute and chronic viral hepatitis and other liver diseases were ruled out. The CA 19-9 tumor marker was negative. In addition, the requested abdominal ultrasonography revealed no abnormalities, with no calculi, normal echogenicity of the hepatic parenchyma, and no signs of chronic disease or portal hypertension. Considering the hypothesis of Caroli’s disease due to recurrent cholangitis in the patient’s childhood and adolescence, magnetic cholangiography was performed, which revealed cystic saccular dilations in the intrahepatic biliary tract (images I, II and III).

Therefore, the patient was led to update the vaccination card, in addition to receiving guidance for the prevention of viral hepatitis. It was decided to withdraw the prophylactic antibiotic therapy, considering the absence of cholangitis in the last three years. There were also guidelines for maintaining the semiannual outpatient follow-up, with face-to-face consultation and complementary exams (USG of the abdomen, CA 19-9 dosage and liver function tests), allowing any worsening of the disease (such as malignant evolution) to be identified in time.
LITERATURE REVIEW

Considering the pathophysiology of Caroli’s disease, it is observed that its main complications include lithiasis in the biliary tract and biliary stasis, both of which are triggering factors for infection (cholangitis). In patients with DC, these infections may recur, being the main manifestation of the disease. Recurrent cholangitis is still an important cause of morbidity and mortality, resulting in a worse prognosis for patients who manifest this spectrum of DC. Other complications include liver abscess formation, sepsis and intrahepatic stone formation after an episode of acute cholangitis, and increased relative risk of cholangiocarcinoma by 7 to 24% in the long term.

It must be noted that, although DC alterations exist before birth, the presentation of the disease usually occurs between the second and fourth decades of life, with carriers remaining asymptomatic until then. Typical clinical manifestations consist of abdominal pain (mainly in the right hypochondrium), hepatomegaly, hyperbilirubinemia (with jaundice), translating cholangitis, which may even reach gastrointestinal bleeding, ascites and other portal hypertension (HP) stigmas.

As there is no serological marker capable of diagnosing DC, the investigation must essentially proceed with imaging tests. The definitive diagnosis is made when it is possible to visualize that the cystic lesions have communication with the biliary tract. In addition to the pertinent laboratory tests (blood count, C-reactive protein, liver and canalicular enzymes, liver and kidney function, electrolytes, among others), it is the abdominal ultrasonography (USG) that is indicated as the first imaging exam in the diagnostic investigation of cholangitis. The greater importance of USG

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1 Magnetic cholangioresonance images showing saccular dilations in the intrahepatic bile ducts, whose multiple nature or diffuse involvement characterize Caroli’s disease (or type V cysts, according to Todani's classification for congenital choledochal cysts).
lies in ruling out differential diagnoses. This has little value in the case of DC, since the findings reveal complications of the disease (such as signs of HP or possible lithiasis), in addition to nonspecific signs (hyperechogenic liver parenchyma, with intrahepatic anechoic content), that do not elucidate the etiology of the infection. On the other hand, computed tomography of the abdomen can be enriching, since it is capable of showing hypodense cystic images (“dotsigns” or central points) with hyperdense content in the biliary tract, which are highly suggestive of DC. Differential diagnoses include primary sclerosing cholangitis, recurrent pyogenic cholangitis, polycystic liver disease, choledochal cyst and biliary papillomatosis. The most sensitive diagnostic method is endoscopic retrograde cholangiopancreatography (CPRE), however, because it is an invasive test, not free of serious complications (of which acute pancreatitis, sepsis and hemorrhages are highlighted, resulting in a poorer prognosis) and high cost, CPRE is reserved for cases of diagnostic doubt and as a prior alternative to surgical treatment, when this is possible. The same complications occur with transhepatic cholangiography, so its application remains restricted. On cholangiography, well-established features that suggest DC are saccular and fusiform dilations of the intrahepatic bile ducts. There may also be abnormalities in the walls of the bile ducts and intrahepatic lithiasis. A study conducted by Levy et al, in 2002, showed that 53% of the analyzed patients had dilations of the extrahepatic bile ducts, and 100% had abnormalities of the intrahepatic bile ducts. Ultimately, this study also showed that the radiological spectrum of Caroli’s disease ranges from diffuse biliary dilation focal to segmental, with dilations of saccular and fusiform appearance, and affecting only the intrahepatic bile ducts or with concomitant involvement of the extrahepatic bile ducts.

Currently, magnetic cholangioresonance is the method of choice for the diagnosis of DC, because it is a non-invasive test that has proven to be effective in the investigation of biliary obstructions. In addition, a good correlation has already been established between the findings of cholangiography and CPRE, since cholangioresonance reveals similar findings. Among these, the following stand out: diffuse large cystic ectasias, diffuse small cystic ectasias, diffuse fusiform dilations, fusiform dilation in the left lobe of the liver, monoliform dilations (where cysts cannot be distinguished from saccular dilations) in the left lobe. It is also possible to complement the investigation with excretory urography and liver biopsy (mainly in the case of Caroli syndrome, in which there is renal involvement and liver fibrosis, and to investigate whether there is congenital liver fibrosis associated with DC) and upper digestive endoscopy. As for the follow-up of these patients, it is necessary to consider that this is a disease whose definitive treatment consists only of liver transplantation. One option for cases in which there are dilatations restricted to a hepatic segment or lobe seems to be liver resection, of which an imaging study is essential for surgical planning. In this case, resection seems capable of reducing the risk of malignancy and the morbidity of recurrent cholangitis. For cases of diffuse disease, or in which evolution to cirrhosis has already occurred, the last and only option is liver transplantation.

Disease progression must be carefully and periodically evaluated on an individual basis to avoid adverse outcomes. Among them, cholangiocarcinoma stands out, whose incidence is one hundred times higher in DC patients compared to the general
population. It is believed that this increased risk of neoplasia is due to prolonged exposure to unconjugated bile salts and carcinogens in the diseased biliary tract. Thus, based on the clinical experience of specialist physicians, it is prudent to perform semi-annually, for an indefinite period, abdominal ultrasound associated with the measurement of the tumor marker CA 19-9. It is also customary to carry out laboratory tests that show hepatocellular or canalicular injury at the same frequency, in addition to those capable of pointing out the hepatic synthesis capacity (TAP, albumin, bilirubin). The evolution of the disease can be variable, and depends on follow-up to identify complications, with frequent liver function tests and ultrasound, to control the early appearance of stones and other associated complications.

The treatment of these patients depends on the clinical characteristics of the disease and the location of the biliary abnormalities. Results obtained from studies with surgical options, such as resection of the affected hepatic segment or internal surgical bypass (bypass) were discouraging, and more research is needed. The effectiveness of these therapeutic proposals. On the other hand, in the presence of lithiasis, a study carried out in 1993 by Ros E et al revealed remission of symptoms, with improvement in liver function and even disappearance of intrahepatic gallstones in patients using ursodeoxycholic acid (300 mg, twice a day). Another pharmacological alternative consists of administering prophylactic antibiotic therapy, empirically, in order to prevent cholangitis. It is ideal that coverage be made against gram negative and anaerobic microorganisms, responsible for most cases of bacterial cholangitis. In the reported case, the patient used ciprofloxacin associated with sulfamethoxazole with trimethoprim for three years, which was discontinued (also empirically) after remaining asymptomatic for this period. This practice needs further studies to be better established, since some point out that prophylactic antibiotic therapy has benefits for some patients, while in others, this remains a controversial fact. Broad-spectrum antibiotics are indicated in episodes of acute cholangitis, but due to anatomical abnormalities of the bile duct, it is possible that permanent sterilization will not occur.

**DISCUSSION**

Although identified and described decades ago, Caroli’s disease remains a challenge in the treatment and management of affected patients. These are abnormalities of the bile ducts, with saccular, fusiform and multifocal dilations, causing impaired bile flow, which predisposes to the formation of multiple calculi that are deposited in the sacculations or impact the common bile duct, leading to cholangitis.

This study demonstrates the importance of magnetic resonance cholangiography in the safe diagnosis of CD. It is currently preferred over ERCP because it is not an invasive method and has a lower cost.

The initial therapy in the reported case was the prevention of recurrent bacterial cholangitis with periodic administration of antibiotics, which proved to be effective in some patients, but because it did not eliminate the underlying disease, it was completely ineffective in others.

Outpatient follow-up, with emphasis on USG and measurement of markers, still require further studies to be precisely determined. In the HSCMV hepatology service, they are performed according to the medical experience of the heads of the service. The need for serial follow-up with USG and laboratory tests is well known.

Liver resection for localized CD is a highly valuable treatment, with the possibility of
cure in patients who have segmental biliary abnormalities\textsuperscript{10}, through segmentectomy or lobectomy\textsuperscript{4}. In the diffuse forms of CD or in the presence of liver fibrosis, orthotopic liver transplantation is the treatment of choice\textsuperscript{4}, being the only curative option\textsuperscript{11}.

It is also worth noting the rarity of this disease in childhood\textsuperscript{9}. Carriers are usually asymptomatic from 5 to 20 years of age\textsuperscript{10}, unlike the age of presentation of the reported patient, whose first episode was at nine years of age. In addition, the patient in this case has a curiously benign evolution of the disease, something considered atypical by the current literature\textsuperscript{9}.

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