

Caroli's disease: 6 case studies

SUMMARY

Caroli's disease is characterized by congenital non-obstructive dilatation of the intrahepatic bile ducts of undefined etiology. It is a rare disease usually affecting the whole liver but it may affect a lobe or a segment (11).

This study shows the evolution of 6 cases (2 boys and 4 girls) that were diagnosed with Caroli's disease at a referral service. Their ages ranged from 2 to 16 years – median age 10 years. One of the patients presented with cholangitis, while hepatomegaly was observed in 83% of the cases. Four of the patients presented biliary lithiasis and in one of these cholesterol crystals could be observed in the duodenal secretion. The diagnosis was confirmed in 4 cases by endoscopic retrograde cholangiopancreatography, in 1 by cholangioresonance and 1 by echography. Two of the patients also presented congenital hepatic fibrosis. The outpatient clinic follow-up indicated that all the patients evolved well with the exception of one patient who was selected as a candidate for liver transplantation.

INDEX: Caroli's disease; diagnostic; treatment.
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INTRODUCTION

In 1958 Jacques Caroli (apud 17) described a clinical condition characterized by congenital saccular or cystic dilatation of the intrahepatic bile ducts, a high incidence of cholangitis and biliary lithiasis, absence of cirrhosis or portal hypertension and association with tubular ectasia or other renal cystic diseases.

This disease has been recognized as a distinct clinical entity since 1964, when Caroli and Corcos (4) conducted an extensive review. Thereafter, sporadic reports have been published (23). The prevalence of this disease is rare – 1 case per million inhabitants (11).

Caroli's disease usually affects the entire liver but occasionally involves only one lobe or a segment. There are some reports of its association with other abnormalities as duodenal diverticulitis, testicular ectopia, hypospadias, acute pancreatitis and the Laurence-Moon-Biedl syndrome (11).

Family cases have been reported and inheritance was considered to be recessive autosomal; however, some authors suggest a dominant inheritance in some cases (23).

The prognosis is poor and a standard approach for therapeutic management has been proposed (13).

The purpose of this study is to report the experience obtained at a referral service by showing the presentation and evolution of 6 cases diagnosed with this rare pathology.

CASE REPORTS

Case 1: D.F.A., 4 years old, white, male, presented at the age of 1 year with a history of increased abdominal volume and hepatomegaly since the age of 1 month. There was no relevant medical history. The physical examination revealed an anicteric child with palpable firm liver 5 cm below the right costal margin (RCM); the spleen was not palpable. Laboratory tests of this patient and others are shown on table 1 and the history and physical examination results on table 2.

An abdominal ultrasonography was carried out and revealed heterogeneous parenchyma and dilatation of the intrahepatic ducts. A Computerized Tomography (CT) showed hepatomegaly, heterogeneous lesions in the right lobe and diffused dilatation of the intrahepatic bile ducts. Histology revealed the presence of hamartomatous ducts and endoscopic retrograde cholangiopancreatography (ERCP) showed sacculatation of the common bile duct and intrahepatic bile duct compatible with Caroli's disease. In the follow up the patient started ursodeoxycholic acid therapy for intrahepatic lithiasis. He remained asymptomatic.

CASE 2: L.F.R., 10 years old, black, female. She was referred at the age of 10 because of an increased abdominal volume. She didn't have an important medical history and presented a palpable firm liver, 5 cm below the RCM and the spleen was 3cm below the left costal margin (LCM). No signs of portal hypertension were found at the endoscopy. The abdominal echography showed increased liver volume with heterogeneous parenchyma, dilatation of the intrahepatic bile ducts and multiple hyperechogenic images. The histology revealed portal fibrosis, hamartomatous alterations of the intrahepatic bile ducts and mild proliferation of the bile ducts. The intraoperative cholangiography suggested Caroli's disease. The CT showed a liver shaped in lobes with a blunt edge and irregular bile ducts. Splenomegaly was also confirmed. The patient was put on ursodeoxycholic acid and has been doing well.

CASE 3: A.O.M., 16 years old, white, female, was first examined at the age of 14. She had a history of blood transfusion because of anemia when she was one year old and had also had splenomegaly since that age. She suffered 2 cholangitis episodes (at the age of 12 and 13 years) and a liver biopsy with congenital hepatic fibrosis. Physical examination revealed an anicteric girl with enlarged firm left liver lobe (3cm below the xiphoid appendix) and the spleen 7 cm below the LCM. Abdominal echography

showed a heterogeneous hepatic parenchyma with hypertrophic left lobe and splenomegaly, besides increased left kidney with lithiasis. Hepatic histology (performed during a cholangitis episode) evidenced portal fibrosis with septal formation, hamartomatous bile ducts and purulent acute cholangitis. ERCP displayed multifocal ectasia of the bile ducts (mainly in the right liver lobe) compatible with Caroli's disease. After diagnosis the patient has had 3 more episodes of cholangitis and is now a candidate for a liver transplantation.

CASE 4: A.F.M., 10 years old, white, female. She has had hepatosplenomegaly since the age of seven and was referred for investigation because her sister was diagnosed with Caroli's disease (case 3). Her medical history shows she had acute lymphoid leukemia when she was seven years old and is out of therapy. Physical examination revealed an anicteric girl with enlarged left liver lobe (6 cm below the xiphoid appendix) and the spleen 6 cm below LCM. Abdominal echography confirmed the physical examination findings and showed dilatation of the intrahepatic bile ducts. The ERCP was consistent with Caroli's disease and an episode of cholangitis occurred after this procedure. At follow up, she's asymptomatic.

CASE 5: A.S.A., 13 years old, black, male. Presented at the age of 12 with a history of pain in the left hypochondrium, slight fever, vomiting and choluria for a month. His medical history included a similar condition one year before but it wasn't investigated. Physical examination showed no alterations. A month afterwards he checked in our emergency clinic with intense epigastralgia accompanied by vomiting and choluria. The abdominal echography showed intra- and extrahepatic biliary lithiasis, enlarged pancreas and dilatation of the Wirsung duct. Scintigraphy revealed hepatic normal function and dilatation of the intra and extrahepatic ducts. Cholangioresonance was performed because there was high probability of cholangitis as a result of ERCP and suggested diffused Caroli's disease. After 40 days, he was discharged. An analysis of the duodenal secretion indicated the presence of cholesterol crystals and ursodeoxycholic acid was introduced. In follow up he is well.

CASE 6: E.S.T., 6 years old, white, female. She was referred with a history of 2 episodes of abdominal pain associated with vomiting since she was 4 years old. Physical examination revealed an anicteric girl with hepatomegaly. Abdominal echography showed dilatation of intrahepatic biliary tree (mainly right liver lobe) with associated lithiasis.

DISCUSSION

Caroli's disease is a rare pathology that is characterized by cystic or saccular nonobstructive dilatation of the biliary

ducts. Its etiology, however, remains undefined.

In 1926, Hamar (apud 2) described the ductal plate as an embryological characteristic of the biliary tract development (2). Later Jorgensen (apud 7) proposed that the biliary duct cysts might result from ductal plate abnormalities. Recently, Desmet stated that almost all the intrahepatic biliary duct congenital diseases resulted from the lack of remodeling of the ductal plate and mature tubular ducts. In Caroli's disease, there seems to be a total or partial interruption of the remodeling (7). The symptoms may appear at any age. In some patients, it is not identified until the age of 50-60 years. On the other hand, especially in the very young, the clinical course is severe in spite of modern therapeutic (22). In 1997, Keane & collaborators (9) related a neonatal case of Caroli's disease. In our series, 2 patients presented symptoms during the first year of life (Case 1 & 3). The cases were diagnosed between the ages of 2 to 14 years (median 10 years). The female gender was slightly predominant (4/6), which is in accordance with literature (1,2,24).

Despite the symptomatic cases, the clinical manifestations could be jaundice, dark urine, pain in the right hypochondrium and episodes of cholangitis. In other cases, it could start as portal hypertension with complications resulting from hepatic fibrosis (13). Vázquez-Iglesias & collaborators (24) reported fever and abdominal pain as the main symptoms, with or without jaundice. Only two patients in this report had cholangitis as initial presentation. Fever was a rare symptom (1/6). Abdominal pain was present in 3 cases. Physical examination revealed hepatomegaly in the majority of the cases (5/6), which was in accordance with literature (2,17,21,23). Association with splenomegaly was found in 50% (3/6).

The diagnosis is based on the confirmation of communication between cystic and biliary tract dilatations (2). The laboratory shows a cholestatic pattern with an increase in bilirubin and alkaline phosphatase (13). Invasive methods were no longer required to reach a precocious diagnosis as this could be obtained using diverse methods of imaging techniques. Therefore, abdominal echography and computerized tomography were used to complement laboratory findings.

The sonolucent spaces, converging toward the porta hepatis within the liver are characteristic of a typical echographic pattern. In 1986, Marchal et al (12) described a new sonographic sign of Caroli's disease. It consisted of portal radicles partially or completely surrounded by dilated bile ducts. This finding was also observed by other researchers (21).

Specific findings using computerized tomography have been described (5,20). Scintigraphy is another method utilized (3,8). The above methods are very useful in diagnosis but cholangiographic ones seem to be better (13) and those commonly used are intravenous cholangiography; percutaneous cholangiography (9); endoscopic retrograde

cholangiopancreatography (24); cholangioresonance (15). The latter will be more commonly used in the future as the contrast injection for endoscopic or percutaneous methods presents a high risk for biliary infection (14). One patient in this study presented post ERCP cholangitis. The disease can be complicated by cholangitis, intrahepatic lithiasis, liver abscess, septicemia and cholangiocarcinoma (7% to 14% of the cases) (2). The favorable results of ursodeoxycholic acid are due to the fact that the stones in Caroli's disease are rich in cholesterol (16). Four of the cases in this study developed intrahepatic lithiasis and in one of these cholesterol crystal could be observed by duodenal tubage.

Associations with congenital hepatic fibrosis (CHF), childhood renal polycystic disease, hypospadias, renal tubular ectasia and common cysts of the biliary duct have been described (11). Two of the cases in our series showed association with CHF and 2 others showed renal alterations. Once the case has been diagnosed and the treatment defined, the extension of the process as well as associated pathologies should be studied.

Hepatic resection, frequently of the left lobe, is the treatment of choice for localized conditions. When one part of the liver is more affected, some authors recommend large hepatectomies removing the most affected lobe. Up to this time there is no satisfactory treatment for the diffuse condition. Biliodigestive anastomosis was proposed but it has not proved to be successful. The use of Fogarty or Dormia catheters, oral administration of chenodeoxycholic acid or intraductal monoactoin perfusion to remove the calculi have been proposed (11). In 1995, Triapepe & collaborators (22) proposed washing the stones with saline solution using a T-tube. This method was effective for the larger ducts.

Long term prognosis is related with the cholangitis episodes. During the bouts of cholangitis, the treatment is done with antibiotics. Some authors have used antibiotics on a daily basis, as a prophylactic treatment with good results (23).

Up to this time liver transplantation has been the most effective treatment for diffused forms, despite the high cost and long term immunosuppressive therapy (13). There are few reports of liver transplantation (18,19). We suggest that the procedure should be considered in the diffuse type of the disease with repeated episodes of cholangitis impaired hepatic function, as in case 3. The difficulty remains in choosing the appropriate time to perform the transplantation.

Despite its low frequency Caroli's disease should be remembered in cases of repeated cholangitis, even without biliary lithiasis. It is also important to investigate the whole family, as dominant autosomal inheritance may exist (23). Multicentric studies are needed to clarify the controversies regarding the treatment and evolution of this disease.

Table I. Laboratory investigation of 6 Caroli's disease cases showing the higher rates in relation to normal values (AST, ALT, FALC, GGT, COL, ALB e GAMA) and in absolute hemogram values.

Patient	AST	ALT	FALC	GGT	COL	HB	LEU	PQT	RNI	ALB	GAMA
1	1,3	47	1	0.54	0.69	9.6	8700	228000	NR	0.67	0.78
2	3	2,6	4	6	0.81	11	10200	301000	1.0	0.88	1,4
3	1,8	1	0.15	0.66	NR	11.4	5400	60000	NR	0.80	1
4	0.77	0.58	1,9	0.72	NR	12	2010	43400	1.4	NR	NR
5	8,7	10	1,2	7,3	0.85	12	22200	248000	1.28	NR	NR
6	1,6	3,2	1,8	9,5	NR	NR	NR	NR	1,07	NR	NR

AST= aspartate aminotransferase (in U/L); ALT= alanine aminotransferase (in U/L); FALC= alkaline phosphatase (in U/L); gGT= gammaglutamyltransferase (in U/L); Col= cholesterol (in mg/dL); Hb= hemoglobin (in g/dL) ; LEU= leukocytes; PQT= platelets; ALB= albumin (in g/dL); GAMA= gammaglobulin (in g/dL); NR= not realized.

Table II. Medical history and physical examination of the 6 patients

Patient	Sex	Age at onset	Presentation	Hepatomegaly	Splenomegaly	Lithiasis
1	M	1month	increased AV	Y	N	Y
2	F	7 years	increased AV	Y	Y	Y
3	F	1 year	splenomegaly	Y	Y	N
4	F	7 years	hepatosplenomegaly	Y	Y	N
5	M	12 years	abdominal pain	N	N	Y
6	F	4 years	abdominal pain	Y	N	Y

AV = abdominal volume

Y=Yes; N=No

Resumen

La enfermedad de Caroli es una entidad caracterizada por una dilatación no obstructiva de las vías biliares intrahepáticas de etiología indefinida. Es una enfermedad rara que afecta frecuentemente todo el hígado o solamente un lobulo o segmento.

Este estudio muestra la evolución de 6 casos (2 niños y 4 niñas) que fueron diagnosticados con la enfermedad de Caroli en un servicio de referencia. Las edades variaron entre 2 a 16 años, mediana de 10 años. Uno de los pacientes tuvo colangitis, encuanto hepatomegalia fue encontrada en 83% de los casos. En 4 pacientes fue encontrado litiasis biliar y en uno de ellos fueron observados cristales de colesterol en la secreción duodenal. El diagnóstico fue confirmado en 4 casos por colangiografía retrograda endoscópica, en 1 por colangiorresonancia y 1 por ultrasonografía abdominal. En dos pacientes fue encontrado fibrosis hepática congénita. En la evolución ambulatorial, 5 pacientes evolucionaron bien, a excepción de un paciente que se encuentra en la lista de espera para trasplante hepático.

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