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ORIGINAL ARTICLE

Caroli's Disease: Report of Surgical Options and Long-Term Outcome of Patients Treated in Argentina. Multicenter Study

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Abstract
Background Caroli's disease (CD) management is still controversial.
Aim The purpose of this study is to report the most frequent clinical features, treatment options, and outcome obtained after surgical management of CD.
Methods A voluntary survey was conducted. Demographic, clinical, surgical, and pathological variables were analyzed.
Results Six centers included 24 patients having received surgical treatment from 1991 to 2009. Seventeen (70.8%) patients were female, with average age of 48.7 years old (20–71), and 95.5% were symptomatic. There was left hemiliver involvement in 75% of the patients. Surgical procedures included nine left lateral sectionectomies, eight left hepatectomies, and four right hepatectomies for those with hemiliver disease, while for patients with bilateral disease, one right hepatectomy and two Roux-en-Y hepaticojejunostomies were performed. The average length of hospitalization was 7 days. For perioperative complications (25%), three patients presented minor complications (types 1–2), while major complications occurred in three patients (type 3a). No mortality was reported. After a median follow-up of 166 months, all patients are alive and free of symptoms. CD diagnosis was confirmed by histology. Congenital hepatic fibrosis was present in two patients (8.3%) and cholangiocarcinoma in one (4.2%).
Conclusions CD in Argentina is more common in females with left hemiliver involvement. Surgical resection is the best curative option in unilateral disease, providing long-term survival free of symptoms and complications. In selected cases of bilateral disease without parenchymal involvement, hepaticojejunostomy should be proposed. However, a close follow-up is mandatory because patients might progress and a transplant should be indicated.

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Keywords Liver cyst · Biliary cyst · Caroli's disease · Liver resection · Hepaticojejunostomy

Introduction

Back in 1818, Jacques Caroli described a rare benign congenital disorder characterized by multiple segmental and communicating saccular or cystic dilatations of the intrahepatic bile ducts,[1–3] named Caroli's disease (CD) in his honor. Later on, an autosomal recesive inherited transmission of the disease was recognized, and two major types were described: a simple disease characterized only by the presence of bile duct dilatations and a complex one associated with the presence of congenital hepatic fibrosis (CHF); the latter was entitled Caroli's syndrome.[4,5] The pathogenesis of the disease was associated to a lack of normal involution of the ductal plate at the level of the large intrahepatic ducts in CD. More peripheral interlobular ducts are involved in sclerosing cholangitis and congenital hepatic fibrosis.[6] In 1977, Todani et al. included Caroli's disease as the worst degree (type V) of congenital bile duct cysts.[7] Clinical presentation is related to bile stasis and stone formation, with recurrent cholangitis as the most common presenting symptom. Some authors have reported a high incidence of acute pancreatitis. CHF and biliary cirrhosis are responsible for the development of portal hypertension.[8,9] Diagnosis is usually established by ultrasound, computed tomography (CT) scan, and magnetic resonance cholangiopancreatography[10–12] (MRCP). Even today, literature reports the use of diagnostic endoscopic cholangiopancreatography (ERCP) as a diagnostic method but also as a therapeutic tool in patients with cholangitis.[9,13,14] A wide variety of therapeutic options from endoscopic, percutaneous, or surgical drainage, liver resection or transplantation can be offered to patients suffering from CD. The best treatment to be offered will depend upon the clinical degree of the disease and biliary abnormality localization.[15–17] As far as we are concerned, only six series, with more than 20 cases each, reporting treatment options and long-term outcomes have been published, and the optimal management algorithm is still open for discussion.[13,15,18–22] Therefore, we aim to report the most frequent clinical features, treatment options, and outcome obtained after surgical management as a result of a retrospective multicenter Argentine survey.

Material and Methods

A retrospective voluntary survey aiming to report long-term outcome of patients who received surgical treatment for CD was approved and placed online in the Argentine chapter of International Hepato-Pancreatic-Biliary Association in 2009. The variables included in the survey were: patient demographics, clinical symptoms, and biochemical parameters at presentation, radiologic studies, previous therapeutic nonsurgical interventions, surgical procedures, complications, length of hospital stay, and long-term outcome. Pediatric patients (<15 years old) were excluded from this study. Caroli´s disease diagnosis was performed by clinical parameters, imaging studies, and histopathological findings. Data for evaluation of the hepatobiliary anatomy included ERCP, percutaneous cholangiography, ultrasonography, CT scan, or magnetic resonance imaging (MRI). Extension of intrahepatic disease was defined as unilateral or bilateral, according to imaging studies. Diagnosis of cholangitis was based on the presence of intermittent right upper quadrant pain, intermittent fever, transient jaundice, and increased biochemical markers. The type of hepatic resection was classified according to the International Hepato-Pancreato-Biliary Association classification reported by Strasberg et al.[23] Histopathological analysis was required to include patients in the survey as well as postoperative follow-up. It was considered a positive case of Caroli's disease if one shows the presence of focal dilatations of the intrahepatic bile ducts, predominantly the segmental ducts. Characteristically, enlarged ducts wrap around neighboring hepatic arteries in a crescent-like fashion and are in continuity with the remainder of the biliary system. In Caroli's syndrome, the major ducts of the entire intrahepatic biliary tree, including those of the hepatic hilum, are dilated, and histologic features of congenital hepatic fibrosis are present in the liver corpus.[24] In both cases without resection, the biopsies were evaluated in concordance with the ultrasonography, CT scan, and/or MRI findings and the indirect signs of biliary obstruction and dilatation of bile ducts were compatible with Caroli's disease. The differential diagnosis with other cholestatic disease was established by the correlation between the imagenologic and histopathologic findings.

Among long-term outcome variables requested to be included, the following should be mentioned: laboratory tests, CA 19–9 levels, and ultrasound, performed every 3 months during the first year and then every 6 months until last appointment or death. Statistical analysis was performed using SPSS© v15 for Windows (SPSS Inc., Chicago, IL). Results were expressed in percentages, mean, standard deviation, and range. Categorical variables were compared using Chi-square or *t* test. Kaplan–Meier actuarial survival was obtained.

Results

Six centers included a total of 24 patients having received surgical treatment from 1991 to 2009. Most of the centers

reporting to the survey were located in Buenos Aires (4/2). Seventeen patients (70.8%) were female, with a median age of 48.7 years (range, 20–71 years; Table 1). Symptomatic disease was present in 95.5% of the reported cases, with recurrent cholangitis as the most frequent among the reported symptoms (23/24 patients, 96%), followed by associated symptoms such as right upper quadrant pain in six (25%) and jaundice in seven (29.2%). Seven patients (29.2%) had previously undergone a cholecystectomy for symptomatic gallstones.

Diagnosis was established by means of an abdominal ultrasound (100%), and CT scan, MRCP, and ERCP were performed in 91.6%; 91.6%, and 16.6%, respectively. The three imaging patterns described by Guntz et al., based on aspect and localization of disease, were present in our series (grape bunch type 1, fusiform type 2, and saccular type 3)

The anatomical distribution of CD was unilateral in the majority of the patients included, 21/24 (87.5%), being the left hemiliver the most commonly affected (70.3%), followed by three bilateral (12.5%), and four right hemiliver (16.6%). There was no associated kidney disease reported. The time range between the onset of symptoms and the suggested surgical treatment was 2–60 months (average, 31.7 months). Prior to the definitive surgical treatment, various therapeutic interventions were performed in seven patients (29.2%). Five patients with recurrent cholangitis were treated by endoscopic (1/24, 4.2%) or percutaneous biliary drainage (4/24, 16.7%).

Surgical Treatment

Liver resection was performed in 22 (91.6%) patients. Two patients received Roux-en-Y hepaticojejunostomy. Intraoperative ultrasound was routinely performed in all cases among all centers. According to the disease extent, the surgical procedures performed were:

1. *Unilateral disease*: left lateral sectionectomy in nine patients, left hepatectomy in eight patients, and right hepatectomy in four patients.
2. *Bilateral disease*: right hepatectomy with left intrahepatic bile duct exploration with multiple stone removal and end to side Roux-en-Y hepaticojejunostomy in one patient; cholecystectomy, intrahepatic bile duct exploration with multiple stone removal, liver biopsy, and end to side Roux-en-Y hepaticojejunostomy was offered to two patients.

Table 1 Demographic variables

Age	Max., 71 years Min., 20 years	Mean, 48.7 years
Gender	Female, 17 (70.8%) Male, 7 (29.2%)	

As part of standard liver resection technique, Pringle maneuver was required in seven cases (29.2%). Only four (16.7%) patients required blood transfusion in the perioperative period (three intraoperatively and one at the first postoperative day). There was no patient treated by liver transplant in the present series.

Complications

Postoperative complications occurred in six patients (25%). According to Dindo's classification,[25] three patients (12.5%) presented minor postoperative complications (type I and II) and were treated by conservative measures. Major complications (type IIIa) occurred in 3 patients (12.5%) treated by liver resection, all from the liver cut surface: one choleperitoneum and one intra-abdominal abscess that required surgical drainage due to failure of minimal invasive procedures. Another patient with a biloma was treated by percutaneous drainage. The average length of stay was 7 days (4–21 days). Perioperative mortality was 0%.

Pathological Analysis

Macroscopical examination of the explanted livers showed saccular or fusiform dilatations of segmental or main bile ducts with visible stones. Microscopy was positive for biliary hamartomas, periductal granulomatous reaction, and ductal plate malformation.

The essential diagnosis was established with the presence of focal dilatations of the biliary tree with associated chronic inflammation and peribiliary fibrosis, according to the previous definition. There were two patients with congenital hepatic fibrosis (CHF) and one patient with an associated cholangiocellular carcinoma (CCC). In those cases with bilateral disease, apart from the typical features of CD, moderate fibrosis was found.

Follow-up

At a mean follow-up of 13.8 years (range, 0.68–18.8 years), the 24 surgically treated patients are currently alive. The two patients treated primarily with hepaticojejunostomy are free of symptoms with normal laboratory tests, CA 19–9, and radiologic examinations at 9 and 12 years of follow-up. The patient with incidental CCC is currently alive with no recurrence at 9 months after the operation.

Discussion

Caroli's disease is a rare congenital disorder that belongs to the group of fibrocystic liver diseases characterized by a variable degree of fibrosis and ectasia.[6] The estimated

incidence is less than 1/1,000,000 population.[26] Since the original description, many case reports have been published or included as part of bile duct cysts reports.[27–30] Few series with long-term result reports of more than over 20 cases treated by liver resection or transplant have been published (Table 1). Diagnosis is often delayed, and long periods from the onset of symptoms to the definitive treatment can be frequently seen[20] (2 to 60 months in our study). Unilateral predominance has also been shown by other studies.[9,13,17] In spite of having described a lack of distribution by sex, in our series a female predominance (70.8%) was observed.[14,15,17,18,20,31] Bacterial cholangitis was the most frequent clinical presentation of CD in our patients. We noticed less incidence of acute pancreatitis in comparison with others.[8,9] Diagnosis, as it was reported, was established by ultrasound, CT, and MRCP in most patients. MRCP was used in this study in a higher proportion (89%) than in other recent series.[14,20] Some authors, like Kassahun et al., even today advocate the use of ERCP and the importance of combining it with other image studies.[9,13,14] We preferred not to use invasive diagnostic methods except in the setting of recurrent cholangitis in spite of medical treatment. Therefore, percutaneous biliary drainage was prescribed in 16.7% of our cases. As it was reported by Gillet 10 years ago and more recently by others, 73% to 83% of the patients with CD received numerous interventions before the definitive surgical treatment.[14,20,32] In our study, only 30% had been treated by cholecystectomy and 29.2% by other interventional procedures like ERCP or percutaneous biliary drainage. Some authors advocate a combination of interventional ERCP, extracorporeal shock-wave lithotripsy, and ursodeoxycholic acid treatment.[33]

The optimal timing for surgical management in patients with CD is still a matter of discussion because time and severity in each patient vary substantially.[14] The factors that should be considered to decide the appropriate surgical treatment are localization, extension of the disease, and association of underlying chronic liver disease, such as congenital hepatic fibrosis or biliary cirrhosis, kidney disease, or associated malignancy. As with earlier series, our cases had a higher percentage of localized left lobe disease.[9,13,20,34] Kassahun et al. found 80% of unilateral disease with a nearly equal left–right distribution.[13] Resection seems to be the first surgical option in unilateral CD, and since the disease had predominance on the left side, left side resections are the most commonly described.[8,9,34,35] In cases with bilobar involvement and in the absence of liver fibrosis or cirrhosis, extended liver resections are indicated.[14,17] As shown in Table 1, the association with congenital hepatic fibrosis ranges from 1.8% to 57%, but it is seldom reported. Waechter et al. indicated that the presence of CHF could lead to worsening portal hypertension after resection in patients with CD.[16] Therefore, in the case of hilar involvement, we preferred to propose a surgical drainage; other studies showed 15% to 25% of bile duct excision done in this entity.[13,20]

In cases with bilateral CD without parenchymal involvement or portal hypertension, biliodigestive anastomosis with duct clearance could be an option after ineffective conservative treatment,[3,8,9,15,35,36] but there is some concern associated with the possibility of cholangiocarcinoma development in the long term.[13] In our study, the patient with longer follow-up after biliodigestive anastomosis showed normal liver function and nonprogressive fibrosis at 9-year follow-up. The 4.3% incidence of cholangiocellular carcinoma reported by us is similar to the range published by other series (Table 2).[13,14] Some authors propose liver transplantation under similar conditions. However, liver transplantation becomes the best option in patients with recurrent cholangitis, refractory to conservative measures, secondary biliary cirrhosis, or congenital hepatic fibrosis with portal hypertension, even more in cases with bilateral involvement.[21] Since 2002, several series reported liver transplants for CD.[13,17,20,28,31] The most relevant single-center experience was written by the Pittsburgh group, which included 30 transplants; a report from the ELTR and a report from the UNOS data base[18,21,22] include more than 100 cases. In those reports, secondary biliary cirrhosis and CHF

Table 2 Surgical treatment of CD: published series with >20 patients

Authors	*n*	M/F	U/B	CHF (%)	CHCA (%)	Resection	LTx
Dagli et al. [15]	21	13/8	9/12	57	0	7	0
Pimentel [9]	26	10/16	20/6	NA	0	20	0
Kassahun et al. [13]	33	15/18	25/6	NA	9	29	2
Habib et al. [18]	30	16/14	NA	30	3	0	30
De Kerckhove et al. [22]	110	57/53	NA	1.8	2.7	0	110
Mabrut et al. [20]	33	21/12	26/7	6	6	28	5
Millwala et al. [21]	104	47/57	NA	NA	NA	0	104
Ulrich et al.[8]	40	18/22	32/8	8.1	9	33	4
Current series 2011	24	7/17	21/3	8.3	4.2	22	0

M/F male/female, *U/B* unilobar/bilobar, *CHF* congenital hepatic fibrosis, *CHCA* cholangiohepatocellular carcinoma, *LTx* liver trasplantation, *NA* not analyzed

were the main indications for transplantation, and patient and graft survivals (77% and 72% at 10 years, respectively[21]) were comparable with other etiologies.[18] In spite of the results, there is an agreement that liver transplantation should be the last treatment option.[14] Our series showed that all patients were free from symptoms with normal imaging and serological markers at 13-year follow-up.

Conclusion

CD in Argentina is more common in females with left hemiliver involvement. Delay between onset of symptoms, diagnoses, and surgical therapy is still present. Patients with congenital IHBD dilatations should be referred early for surgical management.

Surgical resection was proposed as the best curative option in unilateral disease, by all centers, providing long-term survival free of symptoms and complications. In selected cases of bilateral disease without parenchymal involvement, hepaticojejunostomy should be proposed. However, a close follow-up is mandatory because patients might progress and a transplant should be indicated.

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