Original Article

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Surgical treatment for monolobular Caroli's disease – Report of a 30-year single center case series

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Summary **Congenital intrahepatic bile duct dilatation (Caroli's disease) is a rare biliary disease. Although multiple reports exist describing its surgical treatment, relatively few have provided long-term follow-up. Prospective data about 25 cases of monolobular Caroli's disease, with liver resection between 1974 and 2016, were retrospectively analyzed. Patient demographics together with postoperative outcomes and long-term follow-up were assessed. Our 25-patient cohort (average age 53.4 years (range: 27-82)) included 20 cases with disease limited to the left lobe, and 5 to the right. The average time interval between first symptoms and final diagnosis was 5 years (range: 0-34 years). The surgical procedures included left lobectomy in 11 cases, left hepatectomy in 8 cases, right hepatectomy in 3, and sub-segmentectomy in 3 cases. Biliodigestive anastomosis was performed in 7 cases. Complications were observed in 3 patients (25%). Metachronous cholangiocarcinoma was observed in one single case, 10 years after initial operation. In conclusion, surgical treatment for monolobular Caroli's disease is effective, with good short-term results and few complications. Median long-term follow-up was 18 months (range: 3-132), with favorable clinical evolution in 96% of patients.**

Keywords: Caroli's disease, monolobular, liver resection

1. Introduction

Caroli's disease (CD), or congenital intrahepatic bile duct dilatation (IHBDD), is a rare congenital biliary disease, without obstruction, that corresponds to type V congenital bile duct cysts in the Todani classification of biliary cystic disease (*1*) (Figure 1).

CD was first described by Caroli and Couinaud in 1958 (*2*) as a mono or bilobar segmental cystic dilatation of the intrahepatic biliary tract without obstruction. In cases of monolobar disease, for unknown reason, the left lobe is more frequently affected. CD predisposes to biliary stasis, resulting in intrahepatic lithiasis and possible septic complications that include recurrent episodes of cholangitis, liver abscesses, septicemia, and ultimately secondary biliary cirrhosis. Caroli's disease may also occur in association with congenital hepatic fibrosis and/or renal malformations. A disease variant, termed Caroli's syndrome, is diagnosed when dilatation is accompanied by symptoms of portal hypertension (*3*).

Further, CD is related to a 100-fold increase risk of developing intrahepatic cholangiocarcinoma (*4*). Therefore, surgical resection is recommended in cases of monolobar CD (*5*), although little is known about the long-term outcome.

The aim of the present study was to analyze short and long-term effects of liver resection in 25 patients with monolobar CD, which constitutes one of the largest single-center studies, covering a 30-year period.

2. Materials and Methods

Data of 25 adult patients diagnosed with CD, and treated at our Swiss tertiary center between January

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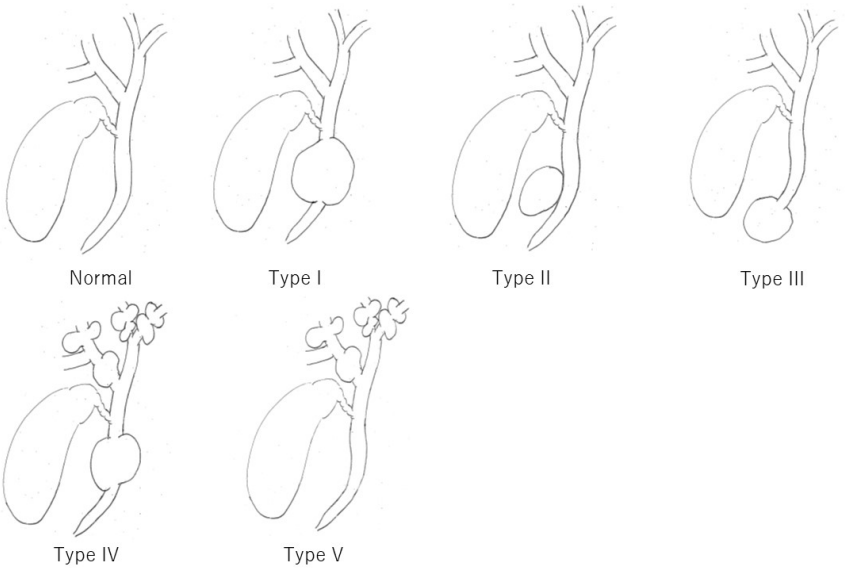

Figure 1. Todani's classification. Caroli's disease (CD) is a rare congenital biliary disease that corresponds to a type V congenital bile duct cyst according to the Todani classification.

1974 and January 2016 were collected prospectively but analyzed retrospectively. Patients' characteristics (gender, age, biological tests, etc.) are summarized in Table 1. Pre-operative imaging was, in the main, by CT, MRI, US, and cholangiography. Primary surgical outcome was our main objective. The final diagnosis of Caroli's disease was confirmed by histo-pathological analyses. The median follow-up time was 18 months (range: 3-132 months).

3. Results

Twenty-five cases of Caroli's disease were included in our analysis, 20 with disease localized to the left lobe and 5 to the right. The present cohort included 10 women and 15 men with an average age of 53.4 years (range: 27-82). The average interval between the onset of symptoms and reaching a diagnosis was 5 years (range: 0-34 years). Symptoms were nonspecific although most patients (17 cases, 68%) presented with the clinical features of cholangitis (abdominal right upper quadrant pain, fever, jaundice, or biological cholestasis). One patient presented with hepatic abscesses, and one with acute cholecystitis (associated with cholangitis due to lithiasis of the main bile duct). One patient was clinically asymptomatic with diagnosis of biological cholestasis (with elevated Gamma-GT and alkaline phosphatase (288 IU/L and 217 IU/L, respectively)) an incidental finding. Previous surgeries for this cohort included cholecystectomy (12 cases), endoscopic sphincterotomy (3 cases), biliodigestive anastomosis (3 cases), resection of a main bile duct diverticulum (1 case), and drainage of a hepatic abscess (1 case). Biliary lithiasis was identified in 20 patients (80%). For 10 (83%) of the 12 most recently treated patients, diagnoses were established by a combination of ultrasonography, cholangiography, CT, and MRI. No detailed diagnostic data were available for earlier cases, treated between 1974 and 1997.

The surgical procedures are summarized in Table 2. Left lobectomy was performed in 10 cases, left hepatectomy in 9 cases, right hepatectomy in 3 cases, and sub-segmentectomy in 3 cases. Biliodigestive anastomosis was performed in 7 cases. This procedure was performed on the biliary convergence after resection of any bile duct tissue showing pathology up to this level.

Histopathological reports of all surgical specimens showed cystic dilatation of the segmental and subsegmental intrahepatic bile ducts, described as irregular cystic cavities ranging from a few millimeters in width to 4 cm, with thick and fibrous walls. In some cases there were also areas of stenosis between 2 adjacent cystic cavities. In all cases, cystic cavities contained black or yellow stones measuring 1 mm to 0.5 cm. In 10 cases, the hepatic parenchyma was of described as normal. In three cases, soft sections at the surface of the cystic dilatation could be depressed at finger pressure. In two cases, the liver was fibrous and pseudo-cirrhotic, which was recognized as congenital hepatic fibrosis. In one case, ectopic intrahepatic pancreatic tissue was found. The biliary epithelium was abraded, almost absent, and in some cases hyperplastic or even papillary. The portal spaces appeared fibrosed and demonstrated infiltration of inflammatory cells with newly formed bile ducts (Figure 2). In one single case (3.7%), a metachronous cholangiocarcinoma was observed 10 years after bisegmentectomy (segment V-VIII) with Roux-en-Y biliodigestive reconstruction.

In the 12 most recent cases (numbered 14 to 25), postoperative complications were rated according to the Clavien classification (*6*).

Table 1. Patient data and therapeutic interventions

Case	Gender, age	Year of diagnosis	Symptoms and year of onset	Year of previous interventions	Previous interventions	Gallbladder lithiasis	Site	Associated lesions	Type of resection
1	M, 34	1974	Cholangitis	1970	Choledocotomy + cholecystectomy	No	L lobe	Intrahepatic pancreatic ectopia	L lobectomy + biliojejunal anastomosis
2	M, 67	1984	Cholangitis	1977	Cholecystectomy	Yes	L lobe		L lobectomy + biliojejunal anastomosis
3	F, 45	1986	Cholangitis	1982		No	L lobe		Subsegmentectomy (III)
4	F, 68	1988	Cholangitis	1959 1981	Cholecystectomy Choledocotomy + surgical sphyncterectomy	Yes	L lobe		L hepatectomy
5	M, 52	1988	Cholangitis, pain			No	L lobe		L lobectomy
6	F, 68	1990	Cholangitis	1974	Cholecystectomy and resection of a diverticulum of the bile duct + bilidigestive anastomosis	No	L lobe	Diverticulum of the bile duct	L lobectomy + biliojejunal anastomosis
7	F, 30	1994	Cholangitis, pain	1994 1994	Endoscopic sphyncterectomy Cholecystectomy	Yes	L lobe		L lobectomy
8	M, 29	1994	Cholangitis		None	No	R lobe	Congenital hepatic fibrosis	R hepatectomy + segment 1
9	M, 49	1994	None, ↑ γ-GT		None		R lobe		R hepatectomy (V-VI-VII)
Case	Gender, age	Year of diagnosis	Symptoms and year of onset	Year of previous interventions	Previous interventions	Gallbladder lithiasis	Site	Associated lesions	Type of resection
10	M, 62	1995	Hepatic abscess, acute pancreatitis	1984 1995	Drainage of abscess and endoscopic sphyncterectomy Cholecystectomy	Yes	L lobe		L lobectomy
11	F, 64	1996	Acute cholecystitis	1996	Cholecystectomy + choledocotomy	Yes	R lobe	Congenital hepatic fibrosis, renal cysts	R hepatectomy + biliojejunal anastomosis
12	F, 69	1996	Cholangitis	1962 1995 1995	Chocystectomy Choledocojejunal anastomosis Biliojejunal anastomosis	Yes	L lobe		L lobectomy + biliojejunal anastomosis
13	F, 27	1997	Pain and recurrent jaundice		None	No	L lobe		L lobectomy
14	M, 61	2001		2001	None	No	R lobe		Subsebmentectomy (VI-VII) + biliojejunal anastomosis
15	F, 45	2001		1999	None	No	L lobe		L lobectomy
16	M, 28	2004		1999	Cholecystectomy	Yes	L lobe		L hepatectomy
17	F, 31	2004	Cholangitis	2004	None	Yes	L lobe		L hepatectomy
Case	Gender, age	Year of diagnosis	Symptoms and year of onset	Year of previous interventions	Previous interventions	Gallbladder lithiasis	Site	Associated lesions	Type of resection
18	M, 40	2005	Cholangitis	2003	None	Yes	R lobe		Subsegmentectomy (V)
19	M, 61	2005	Cholangitis	2001	Cholecystectomy	Yes	L lobe		L hepatectomy
20	F, 29	2005		2005	None	Yes	L lobe		L lobectomy
21	M, 69	2006		2006	Cholecystectomy	Yes	L lobe		L hepatectomy
22	M, 72	2008	Cholangitis	2008	None	Yes	L lobe		L hepatectomy
23	M, 78	2008	Cholangitis	2001	Cholecystectomy	Yes	L lobe		L hepatectomy
24	M, 76	2011		2011	None	No	L lobe		L hepatectomy
25	M, 82	2015	Cholangitis	2015	None	No	L lobe		L hepatectomy

Grades 3 and 4 complication was observed in 3 patients (25%), intra-abdominal abscess, bilioma, and biliary fistula (Table 3). Post-operative 30-day mortality was zero. No precise data about complication was available for cases seen between 1974 and 1997. The median follow-up was 18 months (range: 3-132), with a favorable clinical evolution in most patients (96%).

4. Discussion

To the best of our knowledge, this present study of 25 cases collected since 1974, may be the largest monocentric series reported in Europe.

Differently as in the present series, monolobar form of CD is less commonly encountered. However, as in the present series, left lobe is more likely to be affected (*8*). In fact all 25 patients assessed had localized disease, with 20 patients (80%) presenting left lobe CD, and 5 patients (20%) had CD of the right lobe. The right monolobar subtype is extremely rare in the scarce literature. Without including the present cases, a literature review allowed to identify 31 cases only of right monolobular disease between 1965 and 1994 (*9*). In this present study, the typical CD saccular or fusiform dilatations could be observed by imaging (CT and MRI), with ultrasound (*15*) and CT scans thus suggesting diagnoses prior to surgery. Today, MRI is preferable for non-invasive exploration of the bile duct, as invasive investigations like ERCP carry a risk of infection (*16*).

The most possible serious complication of CD is the development of cholangiocarcinoma associated with biliary stasis, in which (bile) carcinogens and chronic inflammation of the epithelium promote dysplasia. The present series describe one single case 10 year after initial CD diagnosis but a direct relation between CD and cholangicarcinoma still need to be established. It remains hypothetical if genetic lesions in Caroli's disease patients can then ultimately lead to malignant progression.

In the present study, the average interval between becoming symptomatic and an eventual diagnosis was 5 years (range: 0-34 years). The principle clinical features of CD were atypical with abdominal pain, fever attributable to recurrent episodes of cholangitis, and jaundice. A literature review found that recurrent acute cholangitis was the most frequent mode of presentation (64% of the patients) (*7,14*).

In agreement with these studies, right upper quadrant pain and fever, both clinical manifestations of cholangitis, were the most frequent symptoms in our study (68%). Hepatic abscesses and recurrent episodes of jaundice (2 patients) were less commonly reported.

To explain the rarity of reports about CD, it has to be emphasized that this segmental dilatation of bile ducts has an estimated prevalence of 1/1,000,000 (*7*). In the absence of associated congenital hepatic fibrosis, the condition is defined as pure type Caroli's disease (*2*). However, a fifth of all pure CD is associated with cystic dilatation of the common bile duct, and in 6% of cases, congenital hepatic fibrosis (confirmed by histopathology), which was observed in 2 patients in the present series. Bilobar CD, affecting the entire liver, is more frequently associated with congenital hepatic fibrosis, which is responsible for portal hypertension; this condition is Caroli's syndrome and more rare, was not even observed in the present series (*3*).

Multiple pathogenic mechanisms have been proposed to explain CD including both embryologic and acquired factors. The bile ducts form during the 7th week of gestation following differentiation of hepatoblasts into biliary cells. These cells then envelop the vessels of the portal system to form the ductal plate. Subsequently a remodeling process takes place that separates hepatocytes and bile ducts by connective tissue, with the hepatocytes then migrating into the

Table 2. Surgical procedures

Surgical procedure	*n* (patients with biliojejunal anastomosis)	%
Right hepatectomy	3 (1)	12
Left hepatectomy	9 (0)	36
Left lobectomy	10 (4)	40
Subsegmentectomy	3 (1)	12

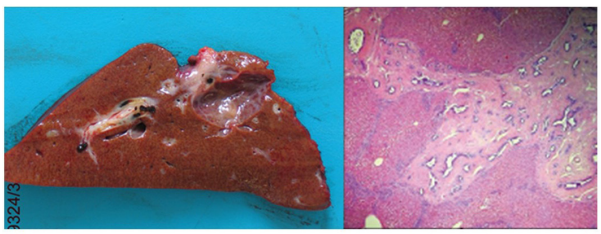

Figure 2. Pathological image. The portal spaces appear fibrosed, and demonstrate infiltration of inflammatory cells with newly formed bile ducts.

Table 3. Postoperative complications in the 12 most recent cases

Complication	Clavien-Dindo classification	Treatment	*n*
Intra-abdominal abscess	IIIa	Drainage	1
Bilioma	IIIa	Drainage	1
Biliary fistula	IIIa	Drainage	1
Liver hematoma	I	Observation	1
Intra-abdominal collection	II	Antibiotics	1

portal spaces. The most plausible pathologic mechanism involves an abnormality of embryonic remodeling associated with excessive cellular proliferation induced by possible genetic lesion (*10*).

This hypothesis is also consistent with the discontinuous and irregular dilatations of the biliary tree typical for this disease. The early onset of this genetic anomaly can result in defects in either the right or left bile ducts, or the segmental ducts (*11*). A later onset could induce lesion formation consistent with that seen in congenital hepatic fibrosis (*12*). Despite some reports of neonatal presentation (*11*), CD usually remains asymptomatic until early adulthood (*13*).

The monolobar disease types (similarly to the diffuse) are usually flagged by cholangitis aggravated by either inappropriate therapeutic interventions or opacification of the bile ducts. The discovery of an isolated lithiasis inside the bile ducts, without lithiasis of the gallbladder, or a diagnosis of cholangitis in a patient with a past history of biliary surgery, should raise a suspicion of Caroli's disease or syndrome, and prompt further investigation ideally with MRI. In the present series, 12 patients underwent cholecystectomy before their final CD diagnosis, and in all cases the postoperative course was uneventful. There was no documented evidence of previously unrecognized damage to the common bile duct during the initial procedure, ruling out episodes of cholangitis secondary to ductal damage during surgery. The present series analysis suggests that despite its rarity, CD should be considered as differential diagnosis in case of recurrent cholangitis.

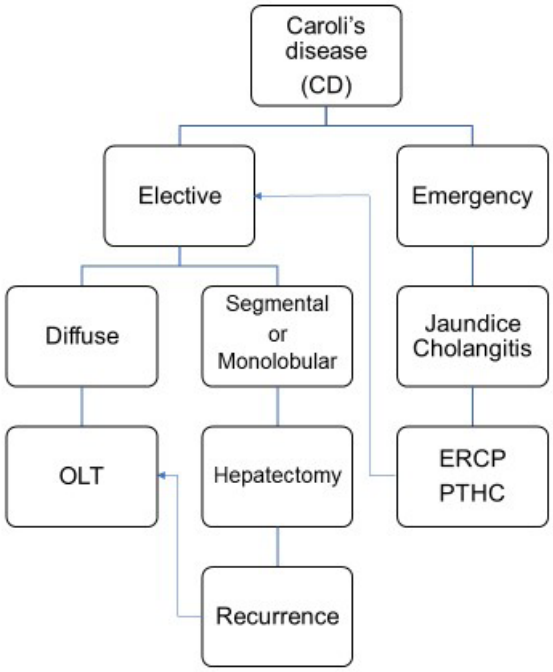

Figure 3: Treatment algorithm for Caroli's disease. ERCP: endoscopic retrograde cholangiopancreatography, PTHC: percutaneous transhepatic cholangiography, OLT: orthotopic liver transplantation

The suggested treatment for monolobular Caroli's disease remain complete resection of the affected regions. Patients with left monolobular Caroli's disease benefit from extended resection including segment IV if this segment is affected as well. For lesions in the right lobe, the extent of resection depends on the segmental anatomical distribution of the biliary ectasia. A Roux-en-Y biliodigestive anastomosis should be performed if the lesion extends to the biliary convergence, thus allowing to restore biliary discharge after surgical resection. Our institutional management algorithm for Caroli's disease is summarized in Figure 3.

While treatment of monolobar CD seems to be well defined, diffuse CD remain challenging, especially if combined approach with partial hepatectomy and biliodigestive anastomosis is impossible (*17*). The alternative in these advanced CD is liver transplantation as the only long-term curative option (*18*). However, in some swell selected case, extended resection may be possible (*18*).

The present study has several limitations to address. The number of patients is relatively modest (n = 25) with a retrospective study design. However, the number of monolobar patients in this study is comparable to those detailed in some recent reports. Ulrich and Mabrut reported 40 CD (monolobar 32, bilobar 8) and 33 (monolobar 26, bilobar 7) patients, respectively (*5,18*).

All series with more than 20 patients with congenital intra hepatic bile duct disease treated by liver resection are summarized in Table 4 (*3,5,18-20*).

In conclusion, surgical resection with an observed acceptable level of post-operative morbidity and here zero mortality, should be considered treatment of choice in monolobar CD. Currently, the diagnosis of CD might be problematic and delayed, because of the complexities in accurately interpreting all symptoms. Even if rare, CD should belong to differential diagnosis of recurrent cholangitis.

Table 4. Series exceeding 20 patients with congenital intra hepatic bile duct disease treated by liver resection

Author (year)	Patients (M/F)	Monolobar (%)(R/L)	Synchronous Carcinoma	Median follow up (months)
Kassahun *et al*. (*19*) (2005)	31 (15/16)	25 (81%) (13/12)	3 (9.7%)	44
Mabrut *et al*. (*18*) (2007)	33 (21/12)	26 (79%) (6/20)	2 (6%)	80
Ulrich *et al*. (*3,5*) (2002/2008)	40 (18/22)	32 (80%) (9/23)	4 (9.1%)	86.5
Mabrut *et al*. (*20*) (2013)	155 (89/66)	107 (69%) (16/91)	8 (5.2%)	35
Current series (2017)	25 (15/10)	25 (100%) (5/20)	0 (0%)	18

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