Surgical Management of Congenital Intrahepatic Bile Duct Dilatation, Caroli's Disease and Syndrome

Long-term Results of the French Association of Surgery Multicenter Study

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Objective: To assess clinical presentation and long-term results of surgical management of congenital intrahepatic bile duct dilatation (IHBDD) (Caroli disease and syndrome) in a multicenter setting.

Background: Congenital IHBDD predisposes to biliary stasis, resulting in intrahepatic lithiasis, septic complications, and cholangiocarcinoma. Although liver resection (LR) is considered to be the treatment of choice for unilobar disease extent into the liver, the management of bilobar disease and/or associated congenital hepatic [brosis remains challenging.

Methods: From 1978 to 2011, a total of 155 patients (median age: 55.7 years) were enrolled from 26 centers. Bilobar disease, Caroli syndrome, liver atrophy, and intrahepatic stones were encountered in 31.0%, 19.4%, 27.7%, and 48.4% of patients, respectively. A complete resection of congenital intrahepatic bile ducts was achieved in 90.5% of the 148 patients who underwent surgery.

Results: Postoperative mortality was nil after anatomical LR (n D 111) and 10.7% after liver transplantation (LT) (n D 28). Grade 3 or higher postoperative morbidity occurred in 15.3% of patients after LR and 39.3% after LT. After a median follow-up of 35 months, the 5-year overall survival rate was 88.5% (88.7% after LT), and the Mayo Clinic score was considered as excellent or good in 86.0% of patients. The 1-year survival rate was 33.3% for the 8 patients (5.2%) who presented with coexistent cholangiocarcinoma.

Conclusions: LR for unilobar and LT for diffuse bilobar congenital IHBDD complicated with cholangitis and/or portal hypertension achieved excellent long-term patient outcomes and survival. Because of the bad prognosis of cholangiocarcinoma and the sizeable morbidity-mortality after LT, timely indication for surgical treatment is of major importance.

Keywords: Congenital, Bile duct cyst, Caroli, liver resection, liver transplantation

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Congenital intrahepatic bile duct dilatation (IHBDD) (Caroli disease and syndrome) is a rare congenital biliary disease corresponding to type V in the Todani classi[cation of congenital bile duct cysts (BDCs).[1,2] The commonly used de[nition for congenital IHBDD was reported by Caroli et al[3] in 1958 and concerned communicating IHBDD of peripheral bile ducts corresponding to type I congenital IHBDD according to the Guntz et al[4] radiological classi[cation. Congenital IHBDD results from abnormal remodeling of the ductal plate responsive to segmental and communicating saccular or cystic dilatation of the intrahepatic bile ducts.[5] The diagnosis of congenital IHBDD is dif[cult to establish because the disease does not manifest by any speci[c histological sign. The only pathognomonic but very inconstant sign is the [central dot sign,[6] which corresponds to hepatic vessels seen within IHBDD after contrast enhancement.[7] Caroli disease (CD) may also occur in association with congenital hepatic [brosis (CHF) (which may result in portal hypertension without liver insuf[ciency) and/or kidney disease (from tubular ectasia to polycystic kidney disease) and then called Caroli syndrome (CS).[1] When associated with CHF, IHBDD can also be strongly considered as congenital. Without these 2 features (central dot sign and CHF), saccular or fusiform segmental bile duct dilatation may be considered as congenital only when they gradually converge with normal distal and/or proximal intrahepatic bile ducts. IHBDD predisposes to biliary stasis, resulting in intrahepatic lithiasis and septic complications, including recurrent episodes of cholangitis, liver abscesses, septicemia, and ultimately secondary biliary cirrhosis. In addition, IHBDD is related to a 100-fold increase of the risk of developing intrahepatic cholangiocarcinoma.[8] Morbidity and mortality are related to infectious and malignant complications. In symptomatic patients, septic and oncological complications are rapidly life-threatening.[3,9,10] The disease-speci[c decision factors for treatment include (i) the extent of the disease into the liver, (ii) whether the lesions are symptomatic or not, (iii) the severity of septic complications, (iv) the presence of underlying liver disease and/or portal hypertension, (v) the presence of an associated kidney disease, (vi) the presence of a synchronous cholangiocarcinoma, and (vii) the risk of long-term malignant degeneration. Treatment of congenital IHBDD has evolved during time from a palliative approach to a radical approach. Although liver resection (LR) is considered to be the treatment of choice for unilobar disease extent into the liver,[11[15] the management of the extent of diffuse bilobar disease into the liver and/or associated CHF is still challenging, as demonstrated by scarce literature.[16] The aim of this study, conducted by the French Association of Surgery, was to assess clinical presentation, patient survival, and long-term results of the surgical management [LR or liver transplantation (LT)] of congenital IHBDD in a multicenter setting.

PATIENTS AND METHODS

Study Population and Data Collection

A multicenter study focusing on the surgical management of BDCs was conducted under the auspices of the French Association of Surgery. Medical records of 600 patients (including demographic data, prior surgical interventions for hepatobiliary and pancreatic (HBP) disease, clinical symptoms, biochemical and imagery examinations, operative data, histopathology reports, duration of follow-up, and long-term outcomes) were retrospectively collected using online computerized standardized questionnaires (http://www.chirurgie-viscerale.org). If necessary, additional data were obtained from e-mail exchanges or phone calls with the referral center. A total of 106 patients presented with type I to type IV-B Todani BDCs and 194 with type V Todani BDCs. The medical and histopathology records and the imaging studies of the 194 patients presenting with bile duct dilatations strictly limited to the intrahepatic biliary tree (considered to present with type V Todani BDCs) were systematically reviewed by 3 of the coauthors (J.Y.M., R.K., J.F.G.). Thirty-nine doubtful cases (20.1%) potentially corresponding to acquired IHBDD because of proximal biliary obstruction, such as benign or malignant stricture or obstructive primary intrahepatic lithiasis, were excluded. Finally, during a 33-year time period (between 1978 and 2011), a total of 155 patients were identified to have congenital IHBDD (including CD or CS) and were included in this study. They came from 26 Western surgical centers (including 24 academic centers), and 110 patients (71.0%) were managed from 2000 to 2011.

Definitions

The extent of the disease into the liver (unilobar or bilobar), location and shape of IHBDD, and the presence of central dot sign (Fig. 1) were evaluated after careful review of imaging studies. Patients were then classified into 3 subgroups according to the Guntz et al[4] radiological subclassification of congenital IHBDD: type I corresponds to "grape bunch"-like saccular dilatation of peripheral intrahepatic bile ducts alternating with normal intrahepatic bile ducts (Fig. 2), type II corresponds to fusiform communicating dilatation of large intrahepatic bile ducts, and type III corresponds to saccular communicating dilatation of large intrahepatic bile ducts. Patients were considered to have CS when congenital IHBDD was associated with CHF and/or kidney disease. Complicated clinical presentation was defined by the presence of severe episodes of cholangitis, acute pancreatitis, portal hypertension (ascites, esophageal varices), biliary peritonitis, or associated carcinoma. Patient operative risk was evaluated according to the ASA (American Society of Anesthesiologists) physical status score.[17]

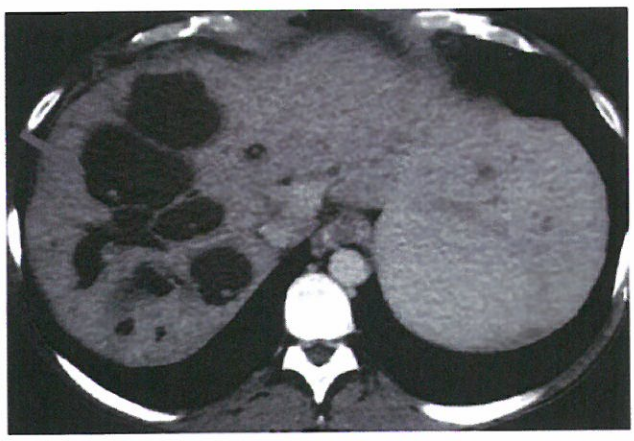

FIGURE 1. "Central dot sign" on computed tomographic scan: contrast enhancement of hepatic vessels within IHBDD (arrow) (Courtesy: D. Castaing, CHB Paul Brousse, Villejuif, France).

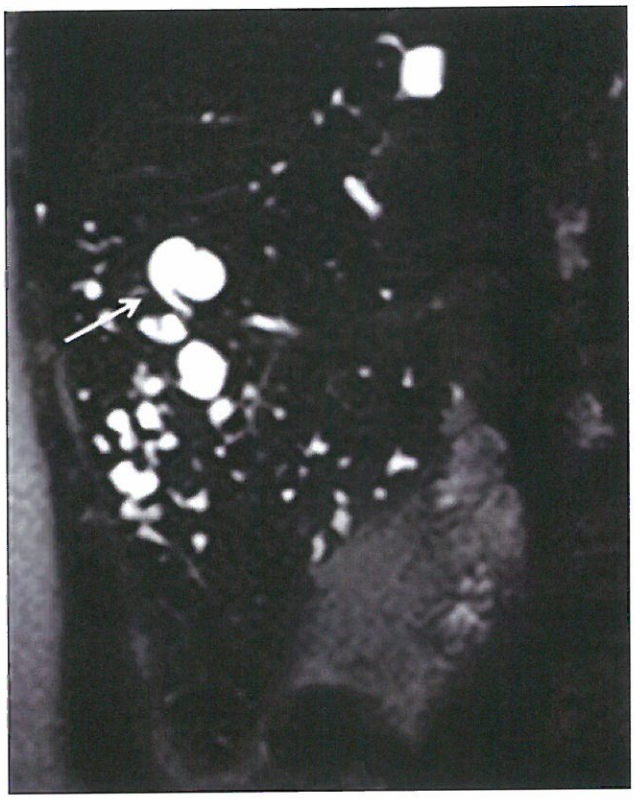

FIGURE 2. Magnetic resonance cholangiopancreatography: T2 sequence. Type I congenital IHBDD with associated CHF (CS).

Postoperative Outcomes

Postoperative morbidity and mortality were defined at 3 months or during hospital stay. Postoperative morbidity was graded according to the Dindo-Clavien classification.[18] Grade III and IV complications were considered as severe morbidity.

Long-term Follow-up

The results for the patients with a follow-up of more than 6 months were evaluated according to a modification of the Mayo Clinic score of results evaluated for congenital BDCs previously reported by one of the coauthors[19]: excellent, if the patient remained free of symptoms without further reintervention; good, if the patient presented with occasional and mild episodes of cholangitis or pancreatitis not impairing the quality of life; fair, if the patient had repeated episodes of cholangitis or pancreatitis or had portal hypertension without further reintervention; and poor, if the patient required later biliary or liver-related surgical procedures, developed biliary cirrhosis or complications because of portal hypertension (such as variceal bleeding), or died of cyst-related malignancy or liver and biliary-related complications. We also reported the results for the patients with a follow-up of less than 6 months.

Statistical Analysis

Data were expressed as median. The χ^2 test was used to compare categorical variables when appropriate (the Fisher exact test was

used when conditions for the χ^2 test were not fulfilled). The Student t test was used to compare continuous variables when appropriate (in case of nonnormality, the Mann-Whitney nonparametric rank-sum test was used). A univariate analysis was performed to assess risk factors for fair and poor long-term results according to the modified Mayo Clinic classification. When significant at the 0.15 level, the factors were entered in a multivariate logistic regression. A Kaplan-Meier analysis was used to estimate the postoperative survival rate. The log-rank test was used to compare subgroups of patients. Statistical analysis was performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC). A P value of less than 0.05 was considered statistically significant.

RESULTS

Demographics/ Patients Characteristics

One hundred fifty-five patients (89 men and 66 women) with a median age of 55.7 years (range, 4–87 years) were included in this study. There were 4 children (2.6%) younger than 15 years. A large majority of patients (88.4%) were Caucasian. Among the 30 patients (19.4%) were classified as having CS, 17 (56.7%) presented with portal hypertension, and 15 (50%) with related kidney disease (tubular ectasia: n = 7; polycystic kidney disease: n = 8). A substantial percentage of patients (54.8%) had a history of surgical and/or endoscopic HBP treatment, significantly more frequently in the CD group than in the CS group (60.0% vs 33.3%; P < 0.01). Forty-five patients (29.0%) experienced intrahepatic stone extraction, and 2 patients (1.3%) previously underwent LR. Only in the CS group, 10 patients (6.5%) presented with a history of biliodigestive anastomosis, 4 (2.6%) with surgical portosystemic shunt, and 2 (1.3%) with kidney transplantation. Thirty-eight patients (24.5%) were at a high risk, being classified as having an ASA score of 3 or more. The summary of preoperative data is reported in Table 1.

Symptoms/ Clinical Presentation

One hundred thirty-nine patients (89.7%) were symptomatic. The median delay between first symptoms and surgical treatment was 7 months (range, 0–500 months). The most frequent symptoms were cholangitis and right upper-quadrant pain. Complicated clinical presentation was seen in 94 patients (60.6%) and was more frequently observed in the CS group (83.3% vs 55.2%; P < 0.01). Indeed, more patients had evidence of cholangitis (76.7% vs 53.6%; P < 0.02), gastrointestinal hemorrhage (23.3% vs 0%; P < 0.0001), and ascites (16.7% vs 0%; P < 0.001) in the CS group, although abdominal pain was more frequent (34.7% vs 6.7%; P < 0.01) in the CD group.

Associated HBP Disease

A coexistent HBP disease was found in 108 patients (69.7%; biliary, 56.8%; hepatic, 47.7%; pancreatic, 4.5%). Hepatic associated diseases were more prevalent (83.3% vs 39.2%; P = 0.0001) in the CS group than in the CD group, and CHF was preoperatively and histologically proven by biopsy in 22 of the 30 patients (73.3%) with CS. However, unilobar liver atrophy (32.8% vs 6.7%; P < 0.01) and intrahepatic stones (53.6% vs 26.7%; P < 0.01) were more frequently encountered in the CD group. At final diagnosis, CHF was observed in the CS group and 8 patients (5.2%; 7 in the CD group and 1 in the CS group) presented with synchronous carcinoma.

Radiological Findings/ Diagnostic Procedures

The diagnosis and extent of the disease into the liver were mostly established by magnetic resonance cholangiopancreatography (74.7%) and/or endoscopic retrograde cholangiopancreatography (27.7%). One hundred seven patients (69.0%) presented with the extent of the unilobar disease into the liver with a predominant localization in the left hepatic lobe (91 of 107 patients). Forty-eight patients (31.0%) presented with the extent of the bilobar disease into the liver, which was more frequently observed (76.7% vs 20.0%; P < 0.0001) in the CS group. According to the Guntz et al[4] classification, types I, II, and III were encountered in 28.8%, 52.1%, and 19.2%, respectively, of the 146 evaluable patients. Type I was more frequent (57.7% vs 22.5%) in the CS group, and type II and III in the CD group (P < 0.01). A "central dot sign" was observed in 10 patients (6.5%), and the main biliary convergence was considered to be involved in 10.3% of the patients.

Operative Procedures

One hundred forty-eight of the 155 patients (95.5%) underwent surgery. All 7 patients who did not undergo surgery were in the CS group. Among them, 4 were listed for LT, 1 was scheduled for elective LR, 1 was put under surveillance, and 1 died preoperatively after variceal bleeding. Seventy-five patients (50.7%) had 1 or multiple preoperative treatments. Patients in the CS group underwent significantly more procedures (76.7% vs 44.4%; P < 0.01), mainly because more patients with cholangitis required antibiotic treatments (63.3% vs 23.1%; P < 0.0001). A total of 15 patients (10.2%) underwent preoperative radiological biliary drainage. Surgery was performed electively in 139 patients (93.4%), and in septic and/or in emergency conditions, surgery was performed in 7 (4.7%) and 7 patients (4.7%), respectively. Details of operative procedures are reported in Table 2. Anatomical LR was performed in 111 patients and LT in 28 patients. The indication for LT was bilobar disease complicated by cholangitis and/or portal hypertension in 27 patients (96.4%). The last patient presented with recurrent diffuse intrahepatic stones after prior LR. One patient (3.6%) received a living donor liver transplant, and 4 patients (14.3%) underwent combined liver and kidney transplantation. A laparoscopic approach for LR was conducted in 8 patients (5.4%), all in the CD group, to perform left lateral sectionectomy (n = 5) (converted: n = 1), left hemihepatectomy (n = 2), and segmentectomy 5 (n = 1). LR was unilobar in 92.8% of patients and bilobar in 7.2%. Left-sided hepatectomies were performed in 87.4% of the patients with unilobar disease. LR was more frequently performed in the CD group (85.6% vs 17.4%; P < 0.0001) and LT in the CS group (73.9% vs 8.8%; P < 0.0001). Complete resection of all congenital intrahepatic bile ducts was achieved in 134 patients (90.5%), without significant difference between the CD and CS groups (90.4% vs 91.3%) and whatever the type of hepatectomy performed (95.5% after LR and 100% after LT).

Postoperative Events

The overall postoperative mortality rate was 2.0% and it was nil after LR. Three patients (10.7%) died after LT: intraoperative bleeding in a patient who previously underwent left hemihepatectomy with alcoholization of segment I and 1 patient each from primary nonfunction at day 4 and from acute rejection responsive to secondary multiple-organ failure at day 53. The overall morbidity rate was 47.6%, and severe complications (grade ≥ III) occurred in 18.4% of patients (15.3% after LR and 39.3% after LT), including biliary fistula and hemorrhage after LR in 7.2% and 0.9% of patients, respectively. In the LT group, emergency re-LT was performed in 4 patients (14.3%), because of hepatic artery thrombosis in 2 patients and primary nonfunction and acute rejection in 1 patient each.

Follow-up/ Mayo Clinic Score

The median follow-up lasted 35 months (range, 3–300 months) for the 145 surviving patients after surgery. During follow-up, an additional disease-related procedure was performed in 13 patients

TABLE 1. Summary of Preoperative Data

	CD (n = 125)	CS (n = 30)	Total (n = 155)	P
Median age, yr	58.6	32.7	55.7	< 0.0001
Sex, male/female	71/54	18/12	89/66	NS
ASA score 3	29 (23.2%)	9 (30.0%)	38 (24.5%)	< 0.04
Previous surgical or endoscopic HBP treatment				
Surgical	75 (60.0%)	10 (33.3%)	85 (54.8%)	< 0.01
Cholecystectomy	62 (49.6%)	4 (13.3%)	66 (42.6%)	< 0.001
Choledocotomy	8 (6.4%)	0 (0.0%)	8 (5.2%)	NS
IHS extraction	3 (2.4%)	0 (0.0%)	3 (1.9%)	NS
Biliodigestive anastomosis	8 (6.4%)	2 (6.7%)	10 (6.5%)	NS
Hepatectomy	1 (0.8%)	1 (3.3%)	2 (1.3%)	NS
Portosystemic shunt	0 (0.0%)	4 (13.3%)	4 (2.6%)	< 0.01
Endoscopic				
Sphincterotomy	42 (33.6%)	5 (16.7%)	47 (30.3%)	NS
IHS extraction	40 (32.0%)	5 (16.7%)	45 (29.0%)	NS
Clinical presentation				
Asymptomatic	12 (9.6%)	4 (13.3%)	16 (10.3%)	NS
Symptomatic	113 (90.4%)	26 (86.7%)	139 (89.7%)	NS
Loss of weight	4 (3.2%)	6 (20.0%)	10 (6.5%)	< 0.01
Asthenia	7 (5.6%)	3 (10.0%)	10 (6.5%)	NS
Abdominal pain	43 (34.4%)	2 (6.7%)	45 (29.0%)	< 0.01
Abdominal mass	0 (0.0%)	2 (6.7%)	2 (1.3%)	< 0.04
Jaundice	28 (22.4%)	10 (33.3%)	38 (24.5%)	NS
Cholangitis	67 (53.6%)	23 (76.7%)	90 (58.1%)	< 0.02
Pruritus	4 (3.2%)	0 (0.0%)	4 (2.6%)	NS
Biliary peritonitis	1 (0.8%)	0 (0.0%)	1 (0.6%)	NS
Acute pancreatitis	13 (10.4%)	4 (13.3%)	17 (11.0%)	NS
Ascites	0 (0.0%)	5 (16.7%)	5 (3.2%)	< 0.0001
Gastrointestinal bleeding	0 (0.0%)	7 (23.3%)	7 (4.5%)	< 0.0001
Complicated clinical presentation	69 (55.2%)	25 (83.3%)	94 (60.6%)	< 0.01
Median delay between symptom and diagnosis, mo	6	8	7	NS
Associated HBP disease				
Hepatic	82 (65.6%)	26 (86.7%)	108 (69.7%)	< 0.03
Secondary biliary cirrhosis	49 (39.2%)	25 (83.3%)	74 (47.7%)	< 0.0001
CHF	2 (1.6%)	2 (6.7%)	4 (2.6%)	NS
Unilobar liver atrophy	0 (0.0%)	22 (73.3%)	22 (14.2%)	< 0.0001
Unilobar (right/left)	41 (32.8%)	2 (6.7%)	43 (27.7%)	< 0.01
	(2/39)	(1/1)	(3/40)	< 0.04
Other				
NASH	1 (0.8%)	1 (3.3%)	2 (1.3%)	< 0.01
Polycystic liver	0 (0.0%)	2 (6.7%)	2 (1.3%)	< 0.01
Autoimmune hepatitis	0 (0.0%)	1 (3.3%)	1 (0.6%)	NS
Undetermined cholestasis	1 (0.8%)	0 (0.0%)	1 (0.6%)	NS
Biliary	76 (60.8%)	12 (40.0%)	88 (56.8%)	NS
Biliary lithiasis	75 (60.0%)	10 (33.3%)	85 (54.8%)	NS
IHS	67 (53.6%)	8 (26.7%)	75 (48.4%)	NS
Choledocolithiasis	27 (21.6%)	4 (13.3%)	31 (20.0%)	
Gallbladder	16 (12.8%)	2 (6.7%)	18 (11.6%)	
Pancreatic	4 (3.2%)	3 (10.0%)	7 (4.5%)	
Acute pancreatitis	2 (1.6%)	3 (10.0%)	5 (3.2%)	
Chronic pancreatitis	2 (1.6%)	0 (0.0%)	2 (1.3%)	
Radiological ndings				
Monolobar disease (right/left)	100 (80.0%)	7 (23.3%)	107 (69.0%)	< 0.0001
Bilobar disease	(11/89)	(5/2)	(16/91)	
Guntz classi cation	25 (20.0%)	23 (76.7%)	48 (40.0%)	
Type I	27 (22.5%)	15 (57.7%)	42 (28.8%)	
Type II	68 (56.7%)	8 (30.8%)	76 (52.1%)	
Type III	25 (20.8%)	3 (11.5%)	28 (19.2%)	< 0.01

IHS indicates intrahepatic stones; NASH: nonalcoholic steatohepatitis; NS, not signi cant.
n D 146 evaluable patients.

TABLE 2. Details of Operative Procedures (N D 148)

Operative Procedures	CD (n = 125)	CS (n = 23)	Total (n = 148)	P
Total hepatectomy (LT)	11 (8.8%)	17 (73.9%)	28 (18.9%)	< 0.001
Partial hepatectomy (LR)	107 (85.6%)	4 (17.4%)	111 (75.0%)	
Others	7 (5.6%)	2 (8.7%)	9 (6.1%)	
Anatomical LR (n D 111)				
Bilobar	8 (7.5%)	0 (0%)	8 (7.2%)	
Unilobar	99 (92.5%)	4 (100%)	103 (92.8%)	
Left liver/right liver	88/11	2/2	90/13	NS
Type of hepatectomy				
Unilobar left LR	88 (82.2%)	2 (50%)	90 (81.1%)	
Left hemihepatectomy	38	1	39	
Left hemihepatectomy extended to S1	11	1	12	
Left lateral sectionectomy	35	0	35	
Left lateral sectionectomy extended to S1	3	0	3	
Segmentectomy 2	1	0	1	
Unilobar right LR	11 (10.3%)	2 (50%)	13 (11.8%)	NS
Right hemihepatectomy	4	1	5	
Right anterior sectionectomy	1	0	1	
Right posterior sectionectomy	3	0	3	
Trisegmentectomy S5 S7	1	0	1	
Segmentectomy 5	1	0	1	
Segmentectomy 6	0	1	1	
Segmentectomy 8	1	0	1	
Bilobar LR	8 (7.5%)	0 (0.0%)	8 (7.2%)	NS
Right trisectionectomy	1	0	0	
Right trisectionectomy extended to S1	1	0	0	
Left trisectionectomy	1	0	0	
Left hemihepatectomy extended to S8	1	0	0	
Left lateral and right posterior sectionectomies extended to S1	1	0	0	
Left medial and right anterior sectionectomies	1	0	0	
Left lateral sectionectomy and segmentectomy 5	1	0	0	
Left lateral sectionectomy and segmentectomy 8	1	0	0	
Other (details)	7 (5.6%)	2 (8.7%)	9 (6.1%)	NS
Portosystemic shunt	0	2	2	
Biliodigestive anastomosis	1	0	1	
Extrahepatic bile duct resection	2	0	2	
Right hepatic duct diverticulum resection	1	0	1	
Choledocotomy and stone extraction	1	0	1	
Explorative laparotomy with liver biopsy	1	0	1	
Wedge resection of intrahepatic biliary tumor	1	0	1	
Associated procedures				
Cholecystectomy	52 (41.6%)	10 (43.5%)	62 (41.9%)	NS
Choledocolithiasis extraction	16 (12.8%)	0 (0.0%)	16 (10.8%)	NS
Intrahepatic stone extraction	6 (4.8%)	0 (0.0%)	6 (4.1%)	NS
Biliodigestive anastomosis	21 (16.8%)	10 (43.5%)	31 (20.9%)	< 0.01
Kidney transplantation	1 (0.8%)	3 (13.0%)	4 (2.7%)	< 0.02
Peritoneal carcinomatosis resection	1 (0.8%)	0 (0 .0%)	1 (0.7%)	NS

NS indicates not signi cant.

(endoscopic or radiological biliary stone extraction: n D 7; re-LT: n D 2; LR: n D 2; endoscopic management of biliary stenosis: n D 2). In the LT group, 2 patients underwent a second LT at 35 and 44 months because of chronic rejection and 1 patient with severe persistent cholangitis bene ted from endoscopic intrahepatic stone extraction. In this series, 31 patients (21.4%) had a follow-up of less than 6 months: 18 were alive without complications, 12 were lost to follow-up, and 1 died of cancer recurrence. One hundred fourteen patients (78.6%) had a follow-up of more than 6 months [median: 49 months (range, 6 300 months)] and could be evaluated for the modi ed Mayo Clinic score. Among these patients, 85 (74.6%) were alive without complications, 19 (16.7%) were alive with symptoms, 5 (4.4%) died from events not related to the disease, 3 (2.6%) died from events related to cancer, and 2 (1.8%) were lost to follow-up, without any signi cant difference between the CD and CS groups. According to the modi ed Mayo Clinic evaluation score, excellent, good, fair, and poor late results were achieved in 87 (76.3%), 11 (9.6%), 2 (1.8%), and 14 patients (12.3%), respectively. Excellent or good results were achieved in 98 of 114 patients (86.0%) without any signi cant difference between the CD and CS groups, between the symptomatic and asymptomatic patients (85.3% vs 91.7%), and between the LR and LT groups (86.5% vs 85%). Moreover, in the unilobar group, there was no signi cant difference for the Mayo Clinic score whatever the lobe involved (left or right) and whatever the LR performed (hemihepatectomy or less than hemihepatectomy) in the left unilobar group (n D 86). The univariate analysis showed that preoperative biliary drainage ($P < 0.04$), synchronous carcinoma ($P < 0.04$), and postoperative biliary complications ($P < 0.02$) were associated with poor and fair results. It also identi ed 7 other signi cant factors at the 0.15 level (age, biliary peritonitis, associated

biliary disease, liver atrophy, cholestasis, cytolysis, and surgery in emergency conditions). However, none of the predictive factors were identified by the multivariate analysis.

Patient Survival

Twelve of the 148 patients (8.1%) who underwent surgery died at surgery or during follow-up. The overall 1-, 5-, and 10-year survival rate of our study population was 95.2%, 88.5%, and 81.9%, respectively, without significant difference between the CD and CS groups: hazard ratio (HR), 0.904 [95% confidence interval (CI), 0.197–4.153; log-rank P = 0.897]. The overall long-term survival rate at 1, 5, and 10 years was 96.7%, 96.7%, and 85.6% after LR and was 88.7%, 88.7%, and 74.3% (graft survival rate: 75.8%, 65.5%, and 55.9%) after LT, respectively, without difference between the CD and CS groups: HR, 0.586 [95% CI, 0.0842–4.171; log-rank P = 0.585]. Despite a 10.7% postoperative mortality rate after LT, the long-term survival rate was not significantly different between the patients who underwent LT and those who underwent anatomical LR: HR, 0.489 [95% CI, 0.142–1.681; log-rank P = 0.246].

Synchronous Carcinoma

The incidence of synchronous carcinoma was 5.2% in the present series. The median delay between first symptoms and surgical treatment was 6 months (range, 0–240 months), without any significant difference for the group of patients without carcinoma. No patient had synchronous carcinoma on surgical specimen of total hepatectomy. There were 7 men and 1 woman with a median age of 66.5 years (range, 54–74 years). All patients presented with type II or III in the Guntz et al classification, and 7 were in the CD group. Two patients presented with perihilar carcinoma. Patients underwent LR (left hemihepatectomy: n = 5; left hemihepatectomy extended to segment 1: n = 1; left hemihepatectomy extended to segment 4: n = 1; wedge resection: n = 1), and lymphadenectomy was performed in 7 patients. One patient had localized peritoneal carcinomatosis treated by cytoreduction. A R0 resection was performed in 6 patients, and none presented with lymph nodes involvement. After a median follow-up of 6 months (range, 1–50 months), 4 patients died of recurrence. The median survival was 7 months, with a 1-year survival rate of 33.3%. There was a significant survival advantage for patients without synchronous carcinoma compared with those with synchronous carcinoma: HR, 26.145 [95% CI, 6.218–109.939; log-rank P < 0.001].

DISCUSSION

This multicenter study conducted under the auspices of the French Association of Surgery reports the largest series of patients with congenital IHBDD and treated surgically. In this study, LR for unilobar congenital IHBDD and LT for diffuse bilobar disease complicated with cholangitis and/or portal hypertension led to excellent long-term outcomes and survival rates without any difference between CD and CS.

To assume a correct diagnosis of congenital IHBDD and address the usual limitations of such retrospective study carried out over a 30-year time period, all the clinical, radiological, operative, and histological reports were systematically reviewed in detail by 3 of the coauthors. Consequently, doubtful records of 39 patients (20.1%) were excluded from this study in which more than 70% of the patients were enrolled during the last decade.

At present, radical hepatectomy is considered as the treatment of choice and conservative management[20–25] is limited to patients with diffuse forms of the disease and for whom surgery is contraindicated. LR leads to excellent long-term results for localized forms without underlying chronic liver disease when the impaired intrahepatic bile ducts have been completely resected (Table 3).[11–15,9,26–30] In contrast, a diffuse bilobar disease is more challenging to cure and patients in whom radical LR cannot be performed for IHBDD are candidates for LT (Table 4).[11–14,16,31–37] In the present series, the 5- and 10-year survival rate for the patients who underwent surgery was 88.5% and 81.9% respectively, with functional results considered as excellent or good in more than 85% of the cases according to the modified Mayo Clinic score whatever the type of the hepatectomy performed (LR or LT). Moreover, no significant difference was found in the long-term results and survival rates between the CD and CS groups. Indeed, most of the patients with a unilobar liver involvement underwent complete resection by partial hepatectomy whereas most of the patients with a bilobar liver involvement and/or CS underwent LT, leading to a radical treatment of the disease with an acceptable operative mortality and morbidity, especially taking into consideration the severity of the disease.

This study reports the largest series of anatomical LR for congenital IHBDD (n = 111; almost 90% on the left lobe) with a zero mortality (Table 3). Before surgery, attention should be paid to the evaluation of the disease extension. Indeed, we have previously reported that the performance of hepatectomy smaller than hemihepatectomy due to insufficient evaluation of the diseased liver is associated with subsequent incomplete resection and poor long-term results.[13] However, in the present series, no difference was found concerning the long-term results whatever the extent of hepatectomy (hemihepatectomy or smaller), especially for the left hemiliver. This can be explained by the fact that (i) most patients were admitted in referral centers for liver surgery, (ii) a detailed report of the extent of the disease with magnetic resonance cholangiopancreatography was obtained for more than 70% of patients, and (iii) more than 70% of patients were treated during the last decade. After LR, biliary reconstruction through a biliodigestive anastomosis using a Roux-en-Y loop is indicated only when the main biliary convergence considered to be involved in the disease (10.3% of the patients in this series) has been resected and, in patients with residual intrahepatic stones,

TABLE 3. Series Exceeding 10 Patients With Congenital IHBDD Treated by LR

Authors	Patients (Male/Female)	Unilobar (Right/Left)	CHF	Synchronous Carcinoma	LR (Death)	LT (Death)	Median Follow-up, mo	Status Well at Follow-up
Gillet et al[29] (1999)	12 (6/6)	12 (100%) (3/9)	2 (17%)	0	12 (0)	0		100%
Kassahun et al[11] (2005)	31 (15/16)	25 (81%) (13/12)		3 (9.7%)	27[z] (2)	2 (0)	44	93%
Mabrut et al[13] (2007)	33 (21/12)	26 (79%) (6/20)	10 (30%)	2 (6%)	27 (0)	5 (0)	80	87%
Ulrich et al[14] (2002/2008)	40 (18/22)	32 (80%) (9/23)	3 (7.5%)	4 (9.1%) (4/44[y])	33[z] (0)	4 (0)	86.5	100%
Current series (2012)	155 (89/66)	107 (69%) (16/91)	30 (19.4%)	8 (5.2%)	111 (0)	28 (3)	35	86%

[x]Explorative laparotomy (n = 2).
[y]Additional palliative resection (n = 4).
[z]Contraindication to LT and biliodigestive anastomosis (n = 3).

TABLE 4. Series and Registry Exceeding 10 Patients With Congenital IHBDD Treated by LT

Authors	Center	Sex (Male/Female)	Indication of Overall LT	Median Age, yr	CHF	Combined Kidney and LT	Postoperative Mortality (Loss of Graft)	Survival 1 yr	Survival 5 yr	Survival 10 yr
Registry										
De Kerckhove et al[35] (2006)	ELTR 1968–2003	110 (57/53)	0.2%	39.7	2%	14.5%		89%	86%	76%
Millwala et al[36] (2008)	UNOS 1987–2006	104 (47/57)	0.1%	35.1		7.7%	8.3% (12.5%)	86%	77%	
Harring et al[37] (2012)	UNOS 1987–2011	140 (64/76)	0.13%	35.6				88.5%	80.9%	77.8%
Series										
Habib et al[16] (2006)	Pittsburgh 1982–2002	30 (16/14)		26	30%		14% (17%)	76%	65%	56%
Current series (2012)	FAS 1987–2010	28 (19/9)		36.4	43%	14.3%	10.7% (25%)	88.7%	88.7%	74.3%

ELTR indicates European Transplant Liver Registry; FAS, French Association of Surgery; UNOS, United Network of Organ Sharing.

to allow access to the controlateral hemiliver to achieve biliary stone clearance.[11,13,14] The most common surgical approach for LR of congenital IHBDD is open surgery. However, a laparoscopic approach can be attempted when a left hemihepatectomy or a left lateral sectionectomy is mandatory.[38] In the present series, 8 recent patients underwent laparoscopy and only 1 patient converted to laparotomy. In less than 10% of cases, surgery was performed during emergency and/or in septic conditions nonresponsive to antibiotics. Under these circumstances, the mobilization of the liver can induce a peroperative septic shock, which can lead surgeons to abandon the LR[11,16] or to prefer using an anterior approach with end-stage mobilization of the liver during LR.[13,39]

LT enables (i) a complete resection of diffuse congenital intrahepatic bile ducts whatever the extent, (ii) to treat underlying liver disease, and (iii) to prevent cholangiocarcinoma degeneration. However, LT induces almost 10% of operative mortality (Table 4), with a sizeable severe morbidity (39.3% in this series), and exposes recipients to complications related to immunosuppressive therapy. As previously reported,[13] we recommend LT only in patients with diffuse bilobar forms of the disease complicated by repeated sepsis or to patients with cirrhosis or portal hypertension.[16,34–37,40] This actually represents less than 0.2% of all LT indications[35,36] and offers similar results to patients undergoing LT for end-stage liver disease.[16,35,37] However, the ideal timing to perform LT has to be clari□ed in superinfected patients at the time of surgery. A feature encountered in 14% in the present series and in 46% in the European Transplant Liver Registry.[35] For Habib et al,[16] the occurrence of a preoperative superinfection was considered to be a signi□cant prognostic factor of survival and may justify early consideration of LT during disease progression. Some authors[13,34] have reported a few recommendations to limit the risk of postoperative septic complications in patients who underwent transplant under immunosuppressive therapy: (i) avoiding the performance of invasive preoperative biliary procedures that may increase the risk of biliary superinfection, (ii) performing LT when biliary sepsis is under control, if possible, and (iii) giving prolonged antibiotic therapy after LT. Because of the well-known lack of cadaveric donors and to propose LT on an elective basis, once the sepsis is under control, living donor LT have been proposed as an alternative option for congenital IHBDD (5.0% in the American registry[37]), leading to excellent results both in adults and in children.[12,34,41] In addition, in the present series, 70% of the recipients underwent a biliary reconstruction using a Roux-en-Y loop. However, as CD and CS do not present with pancreatobiliary maljunction,[42] the risk of developing a metachronous cholangiocarcinoma within the extrahepatic biliary system is not increased. In this regard, we do not recommend routine biliodigestive anastomosis during LT for congenital IHBDD. Therefore, choledococholedocostomy remains a valuable option in these patients.

Most importantly, patients with congenital IHBDD are at high risk to develop intrahepatic cholangiocarcinoma, either synchronously or after incomplete resection. The reported average prevalence is close to 7%,[8] but higher values of up to 25% to 30% have been reported (Table 3). The prevalence of cholangiocarcinoma was 5.2% in the present series. This may be underestimated because the present series is a retrospective and multicentric study and therefore patients with malignancy who did not require surgery were not included in the study. A surgical resection is the treatment of choice for invasive lesions diagnosed preoperatively. However, as demonstrated in the present series, the prognosis is poor with a 1-year survival rate of only 33.3%. Most of the time, LT is contraindicated in patients with an invasive preoperatively diagnosed cholangiocarcinoma.[43,44] Indeed, because of the high recurrence rate in patients under immunosuppressive therapy, results of LT in such instances are far below the survival rates for patients who underwent LT for other causes.[45] Intrahepatic cholangiocarcinoma on congenital IHBDD is usually an invasive disease. Because of the dismal prognosis of such patients, early radical resection should thus be encouraged. Regarding the low morbidity-mortality, elective LR should be performed in patients for whom LR could lead to the complete resection of the intrahepatic bile ducts even in asymptomatic patients. However, when an indication of LT is under consideration, the risk of developing and the poor prognosis of cholangiocarcinoma should be balanced with the 10% postoperative mortality rate. Further studies are needed to assess the indication of prophylactic LT in asymptomatic patients with diffuse forms of congenital IHBDD.

When adopting an aggressive surgical approach for congenital IHBDD, LR for unilobar disease and LT for diffuse bilobar disease complicated with cholangitis and/or portal hypertension can result in excellent long-term patient outcomes and survival rates. However, the best timing for surgical treatment is of major importance. Surgery has to be avoided in septic conditions. Because of the high prevalence of septic complications during disease development and the risk and poor prognosis of cholangiocarcinoma, early surgical treatment is recommended and prophylactic LR need to be discussed even in

asymptomatic patients with unilobar form of the disease. However, in patients with diffuse bilobar form of the disease, the sizeable mortality and morbidity rate of LT must be balanced with the risk of cholangiocarcinoma in asymptomatic patients.

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DISCUSSANTS

T. van Gulik (Amsterdam, The Netherlands):

A large multicenter study was conducted by the French Surgical Association and included 26 centers. The only center I missed was one where Jacque Caroli worked as an hematologist. Anyway, it is a tremendous achievement to enroll 55 patients. I think the initiating author should be applauded for conducting such a study on a topic that usually generates some confusion. The data were collected retrospectively over a 33-year time period and, of course, it is difficult to control the data, especially the older data in terms of consistency. Nevertheless, this is the largest series reported and I would like to congratulate the authors for this analysis.

I have a few concerns and a few comments; the first concern is the definition of IHBDD you used. What were the criteria used to determine the extent of the disease? How did you separate the solely intrahepatic disease from the combination with extra hepatic disease? Also, it is quite important to determine involvement of the hepatic duct confluence. That was 10.3% in this series. How was that determined, because it is only in recent times that we have imaging that can precisely indicate whether there is an involvement of the hepatic duct confluence? Intrahepatic lithiasis is a common feature of this disease. How can you distinguish primary bile duct dilatation from bile duct dilatation secondary to stone disease?

An interesting point was that two thirds of the patients had unilobar disease and 85% had disease confined to the left liver lobe. Was there a bias in the study because those patients with disease in their right liver lobe were less frequently referred for surgery because of the extent of the disease or is there actually a predilection of the disease to the left liver lobe? If so, could you speculate on why that would be so?

An important point to note is that 5.2% of the patients with CD presented with synchronous bile duct cancer. Is that a correct estimation of the actual incidence? It may be an overestimation because many people will have CD, which is not identified or an underestimation because many patients who develop cancer will not be referred.

The final thing I would like to discuss is that 90.5% of your patients had a complete resection, so in other words, 10% had residual disease. How long was the follow-up in that 10% of patients? Looking at your survival curves; they did not have cholangiocarcinoma or other problems in their residual disease. What is the clinical significance of leaving behind some of the disease in terms of your extent of resection? I enjoyed reading the paper and would like to thank the association for giving me the privilege of the first discussant.

Response From J-Y. Mabrut (Lyon, France):

Thank you for your comments and your questions. I agree with you regarding the definition of the disease. We used the presence of CHF and bile duct dilatation when the dilatation gradually converges with normal intrahepatic bile ducts, proximal or distal. The definition of Dr Caroli was peripheral secular dilatation communicating with the peripheral bile duct. So when you have dilatation of the bile duct that gradually converges with normal peripheral or proximal bile ducts, we consider that is congenital. When there is stenosis, it could be an acquired dilatation, so these patients were excluded from the study. That is why 20% of patients were not selected for analysis.

With regard to the second question concerning type 4A where there is an association of BDCs and IHBDD, this study was conducted under the auspices of the French Association of Surgery and involved 505 patients, including 155 patients with CD. There were 72 patients with type 4A, and they were analyzed separately.

Concerning the predominance of the left-sided liver disease, I have no answer. But I think that it is probably selection bias because these patients are surgically resectable and so are preferentially referred for surgery when there is less diffuse disease. I am not sure that all patients are referred for surgery, so I do not know the answer.

Concerning the estimation of the incidence of synchronous carcinoma, I'm sure the reason is that it is a surgical series. The overall incidence is probably underestimated because patients who could not be operated on radical intent were not included.

Your last question is very interesting: the follow-up of patients who underwent complete resection. We did compare long-term results between the 2 groups, complete resection or incomplete resection, and we did not observe any significant differences concerning outcome or survival. Follow-up of this is very limited because the median of follow-up is 35 months and is too short to evaluate risks for cholangiocarcinoma.

DISCUSSANTS

H. Bismuth (Villejuif, France):

Thank you Dr Mabrut, my question relate to the 2 types of images that you showed; one is when the large branches are involved, and the second, the branches are normal and there is cystic dilatation of the branches at the periphery. I consider that this one is the real CD. As a resident, I worked with Dr Caroli, who was a pathologist. Caroli said that disease with cystic dilatation is different from dilatation of the branch. So my question is about the difference in the treatment and the prognosis between these 2 types of disease. More precisely, what is the prognosis of patients with peripheral dilatation and with normal branch of the bile ducts inside the liver?

Response From J-Y. Mabrut (Lyon, France):

Thank you very much for your comments and question. We analyzed the patients using subgroup classification type 1, which is a peripheral cystic dilatation (definition from Caroli in 1958) and types 2 and 3 with dilatation of larger bile ducts. Twenty-nine percent of patients had type 1, and we found that these patients are more likely to be associated with CHF and with CS. Concerning synchronous carcinoma, 7 of the 8 patients presented with type 2 or type 3, only one presented with type 1. So cholangiocarcinoma is possibly less important for type 1, but type 1 disease is more frequently associated with CHF, thus needing more liver transplants. Thank you very much.