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ORIGINAL ARTICLE

Liver resection and transplantation in Caroli disease and syndrome☆

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Summary
Introduction: Caroli disease (CD) is a congenital dilatation of the intrahepatic bile ducts. In combination with liver fibrosis or cirrhosis, it is called Caroli syndrome (CS). Infectious complications and intrahepatic cholangiocarcinoma are secondary problems. The aim of this study was to analyse the clinical pattern and outcome in patients with CD/CS who underwent liver surgery.
Methods: Between January 2004 and December 2016, 21 patients with CD/CS were treated with liver resection or transplantation (LTX) and post-operative data of patients with CD/CS were retrospectively analysed in a database.
Results: Two patients underwent LTX, and 19 patients underwent liver resection due to CD/CS. During follow-up, one patient developed lung cancer nine years after LTX. Patients resected due to CD/CS were predominantly females (74%) with an overall low incidence of co-morbidities. The median post-operative Clavien-Dindo score was 1 (range: 0—3). There was no death during a median follow-up period of over five years. In four patients, cholangiocarcinoma was confirmed. Tumor recurrence was seen in three patients, and was treated with chemotherapy or repeated liver resection.
Conclusions: LTX and liver resections due to CD/CS are rare and associated with an acceptable post-operative morbidity and low mortality. Surgical treatment should be performed as early as possible to avoid recurrent episodes of cholangitis or carcinogenesis.

Introduction

Caroli disease (CD), first described by Vachell and Stephens in 1906 [1], was eponymously named by Caroli in 1958 [2], is characterized by the segmental dilatation of the intrahepatic biliary ducts in combination with renal cystic disease. It is believed to be caused by a genetic mutation [3,4]. A malformation of the intrahepatic bile ductal plate with consequently focal inflammation and destruction has been proposed as a possible etiology for the biliary ductal dilatation [5,6]. Both autosomal recessive and dominant modes of inheritance have been discussed [7,8]. The combination of biliary tract dilatation with liver fibrosis is called Caroli syndrome (CS) [9,10].

The clinical presentation varies but often includes right upper abdominal pain, fever, jaundice, pruritus, cholangitis, pancreatitis, weight loss, emesis, diarrhoea, and general

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debility [3,11–13]. When seen in association with liver fibrosis or cirrhosis, signs of portal hypertension are frequently described [12,14]. Furthermore, disease progression with recurrent episodes of cholangitis, abscess, sepsis, pancreatitis, and even development of cholangiocarcinoma complicate the disease [6,7,15].

Liver resection is proposed as a primary treatment option for monolobar disease, in the absence of recurrent cholangitis, liver fibrosis, or cirrhosis [14,16]. Biliary drainage interventions, whether by endoscopy, radiology-guided percutaneous intervention or surgical biliary drainage operations, are frequently associated with morbidity and mortality due to infectious complications and high recurrence rates [13,14,17]. Complicated bilobar disease with liver fibrosis and portal hypertension should be treated with liver transplantation (LTX) [14].

The aim of this retrospective study was to evaluate the clinical pattern and outcome of patients undergoing anatomical liver resection and liver transplantation due to CD and CS in a single hepatobiliary center.

Patients and methods

All consecutive patients undergoing anatomical liver resection or liver transplantation for CD or CS between January 2004 and December 2016 were included in this retrospective analysis. All data were collected from institutional patient records. Ethical committee approval for this retrospective investigation was given by the University of Jena, Germany (No. 4428-05/15).

The operative management was unchanged during the study period. During the operation, the target central venous pressure was <5 cm H_2O during the dissection period. A Cavitron ultrasound surgical aspirator (CUSA, Integra, Germany) was used for hepatic transection without the Pringle manoeuvre.

The following demographic and clinical parameters were assessed: age, gender, body mass index (BMI), Charlson's Co-morbidity Index, American Society of Anesthesiologists (ASA) score, pre-operative symptoms, additional renal pathologies, laboratory values, duration of the operation, extent of liver resection, histological assessment regarding fibrosis or cirrhosis of the liver or cholangiocarcinoma. Post-operative morbidity was assessed by the Clavien-Dindo classification, need for biliary stenting therapy, need for surgical revision, post-operative length of intensive care unit (ICU) therapy, length of hospital stay, in-hospital mortality, long-term survival, and tumor or disease recurrence.

Statistics

All data are expressed as the geometric means ± standard deviations unless stated otherwise. Statistical analysis of the data was performed with the SPSS 20.0 software package (SPSS, Chicago, Illinois, USA) and GraphPad Prism version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Between January 2004 and December 2016, a total of 1175 anatomical liver resections were performed at our center. Nineteen of these patients (1.6% of all resections) underwent anatomical liver resection because of CD ($n=6$; 32%) or CS ($n=13$; 68%, Table 1). Most patients had been treated previously in other hospitals for recurrent episodes of cholangitis and were then transferred to our center for the evaluation of definite surgical treatment. The majority of patients were females ($n=14$; 74%). The mean age was 56 ± 14 years. The body mass index was 27 ± 4 kg/m^2. Charlson's Co-morbidity Index and the ASA score were low (median: 2, range: 0–2 resp. 1–2). Renal cysts were detected in four patients (21%), with impaired renal function in two patients (10%) without the need for dialysis. Sixteen patients (84%) were symptomatic at the time of operation with pain ($n=12$; 63%), fever ($n=5$; 26%) and cholangitis ($n=11$; 58%). Stenting of the biliary tree was necessary in 21% ($n=4$) of the patients prior to surgery and almost all patients underwent ERCP for biliary diagnostic evaluation or treatment ($n=17$; 89%). Pre-operative CA 19-9 levels were found to be slightly elevated, with a mean of 137 ± 313 U/mL.

Table 1 Demographic and technical operation data of patients undergoing liver resection.

	n (% of total)
Female gender	14 (74%)
Age (years)	56 ± 14
Charlson's Co-morbidity Index[a]	2 (0–2)
ASA score[a]	2 (1–2)
BMI (kg/m^2)	27 ± 4
Liver fibrosis	13 (68%)
Renal cysts	4 (21%)
Type of surgery	
Monosegmentectomy	1 (5%)
Left lateral segmentectomy	8 (42%)
Right hepatectomy	3 (37%)
Left hepatectomy	7 (16%)
Duration of operation [minutes][a]	172 ± 49
Weight of resected liver [g][a]	365 (138–1500)

ASA: American Society of Anesthesiologists; BMI; body mass index.
[a] Values are the median (range).

During the same time period, 610 LTX were performed, two (0.3%) of which were necessary because of CS and concomitant liver cirrhosis. One female patient was treated with living-donor liver transplantation and one male patient with cadaver liver donation. The mean time on the waiting list was 269 days, with a MELD score of 6 and 24, respectively. Pre-operative liver biopsy was not performed routinely. However, sites of biliary stricture were biopsied without detection of malignant cells. Both patients had indirect clinical signs of portal hypertension, including splenomegaly and esophageal varices.

Liver resection for monolobar disease

In all patients with biliary dilatation limited to a single lobe, an anatomical hepatic resection was performed, with an incidence of 74% affecting the left liver lobe, mainly segments 2 and 3 (Fig. 1A). A major resection with hemihepatectomy [left $n=7$ (37%), right $n=3$ (16%)] was necessary in ten patients (53%), while nine patients (47%) required a minor resection with monosegmentectomy [$n=1$ (5%)] or left lateral segmentectomy [$n=8$ (42%)]. In one patient, a small tangential gastric resection was necessary due to adherence to the liver lobe (Table 1).

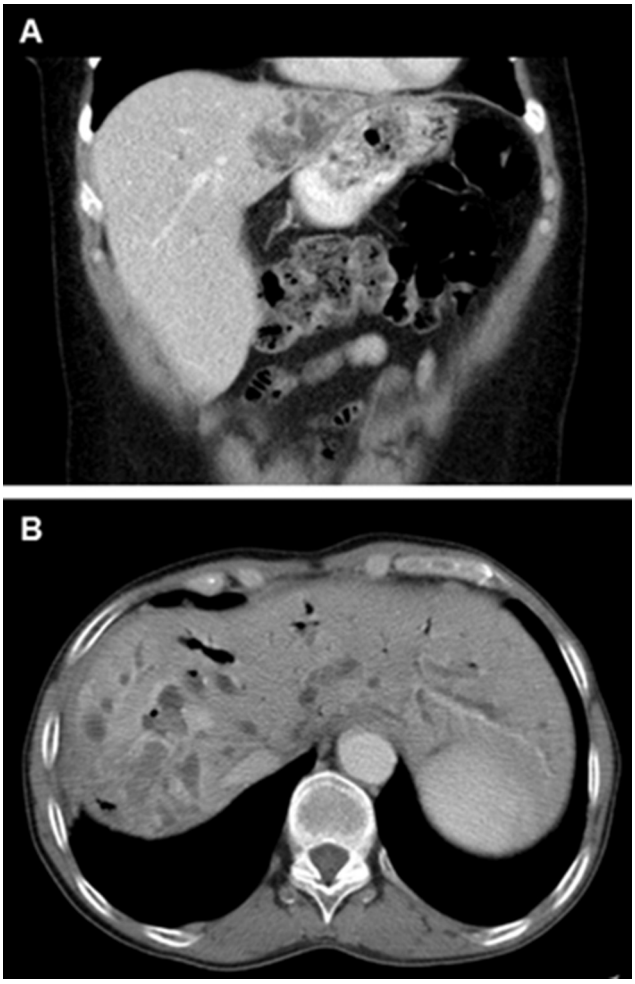

Figure 1. Representative radiological images of monolobar (A) and bilobar (B) dilatation of the biliary system due to CD or CS.

During hemihepatectomy, a hepatico-jejunostomy was necessary in only one patient. All operations were carried out with antibiotic prophylaxis (cefuroxime/metronidazole $n = 18$, piperacillin/tazobactam $n = 1$). The mean duration of the operation was 172 ± 49 minutes. The median weight of resected liver was 365 gm (range: 138—1500 gm). All patients were observed for 24 hours in the ICU except for one patient who was observed for two days. The overall post-operative complication rate was 37%. Complications included biliary leakage ($n = 5$), urinary tract infection ($n = 1$) and pleural effusion with a need for drainage ($n = 1$). The median Clavien-Dindo score was one (Table 2). In three patients (16%), surgical revision was necessary due to biliary leakage and two bilomas (11%) were successfully treated by stenting and drainage of the biliary tree. There were no significant alterations of the kidney function or need for dialysis during the post-operative course. The overall length of the hospital stay was 14 ± 9 days. Pathology examination revealed a cholangiocarcinoma in four patients (21%), whereas, in one patient, a carcinoma was suspected pre-operatively. The tumor stage ranged from T1 to T3, and lymph node involvement was present in one case (Table 3). No patient underwent post-operative adjuvant chemotherapy. Local tumor recurrence occurred in three out of the four patients (75%), with diagnosis of cancer at 10—18 months following the initial surgery (Table 3). Recurrence was then treated either with chemotherapy or repeated liver resection. During the follow-up period of 70 ± 43 months, no patient with cholangiocarcinoma died. The follow-up of patients without cholangiocarcinoma and without mortality or tumor development was 56 ± 34 months.

Table 2 Post-operative complications of patients undergoing liver resection.

	n (% of total)
Clavien-Dindo-Score	
0	12 (63%)
2	1 (5.5%)
3	6 (31.5%)
Biliary leakage	5 (26%)
Surgical revision	3 (16%)
Endoscopic stenting	2 (11%)
Pleural effusion	1 (5.5%)
Urinary tract infection	1 (5.5%)

Table 3 TNM classification and tumour recurrence of patients with cholangiocarcinoma.

	T	N	M	R	Local tumour recurrence
Patient # 4	T3	N0	M0	R0	No
Patient # 7	T1	N1	M0	R0	Yes
Patient # 11	T2	N0	M0	R0	Yes
Patient # 16	T2	N0	M0	R0	Yes

Liver transplantation for bilobar disease and liver cirrhosis

Liver transplantation was required for bilobar disease of CS with concomitant liver cirrhosis and portal hypertension (Fig. 1B). At the time of the transplantation, neither of the two patients had acute cholangitic abscesses or a septic episode. LTX was performed in standard fashion as previously described. The cadaveric liver transplantation was performed with end-to-end cavo-cavostomy and biliodigestive anastomosis. The living-donor liver transplantation was performed using a split right hepatic graft with duct-to-duct biliary anastomosis [18,19]. Post-operatively, the patients were monitored for five days in the ICU, and after 20 and 28 days, they were discharged from the hospital. Initial immunosuppressive therapy consisted of induction with basiliximab and tacrolimus-based immunosuppression. A stricture of the biliary anastomosis occurred two months after the living donor LTX. The stricture was treated successfully with biliary stenting without recurrence during further follow-up. During a follow-up period of eight years, no rejection episode or recurrence of the CS was observed. There was no mortality or evident hepatic tumor detection during follow-up, however, one patient developed lung cancer nine years after LTX.

Discussion

The present study highlights the importance of an early diagnosis of CD and CS in patients who present with episodes of recurrent cholangitis in order to offer the best treatment options including liver resection and liver transplantation. These surgical procedures are associated with an acceptable post-operative morbidity and low mortality. The surgical approach is dependent on the degree

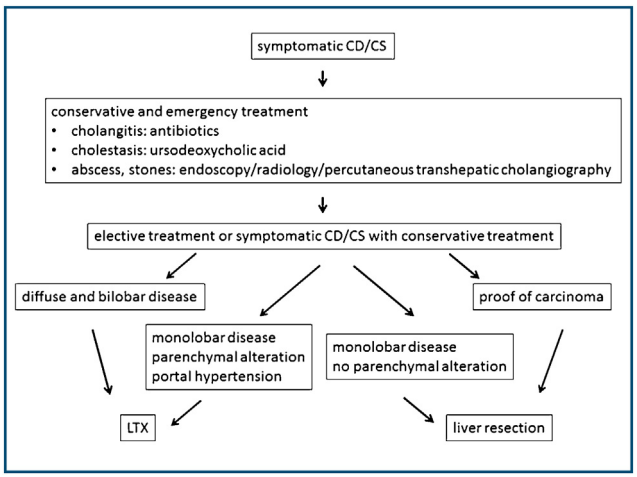

Figure 2. Treatment algorithm for symptomatic Caroli disease (CD) or syndrome (CS) by liver resection or liver transplantation (LTX).

of biliary dilatation and concomitant liver parenchymal damage, such as liver fibrosis and cirrhosis. The surgical treatment should be completed as early as possible to avoid life-threatening complications and to minimize the risk of carcinogenesis [12]. Monolobar disease without alterations of the benign liver parenchyma should be treated with local liver resection. Patients with diffuse and bilateral disease involving parenchymal and functional alterations should be offered LTX [14,16]. On the basis of previous reports and our own experience, we propose an algorithm as shown in Fig. 2.

As CD is rare, with an estimated incidence of 1 per 1,000,000 population, it is important to diagnose CD in case of recurrent cholangitis, especially in patients younger than 30 years of age [20]. The time interval between onset of the disease and definitive treatment may be up to 60 months [12,21]. However, the reported mean age at the time of surgery in the literature and in this study was younger than 60 years and is thus lower than in patients undergoing liver surgery for hepatocellular cancer [21—23]. While no gender predominance is described in the literature, we found that our cohort included substantially more female patients [13,21—23]. A higher frequency of left liver lobe involvement was also reported, as was also seen in our series [3,12,24,25].

As in previous reports, the mortality rate was 0% during the hospital stay and during the further follow-up of about five years after liver resection [21,23]. The overall post-operative complication rate in this study was acceptable and was comparable to that of previous reports [21]. The main post-operative complications were biliary leakage and biloma, which were treated by either interventional or surgical methods. In a recent study, the complexity of liver resection, including segmentectomies and hepatectomies, has been shown to be an independent risk factor for the development of biliary leakages, which might explain the rate of biliary complications in the present study [26]. It has been shown previously that endoscopic procedures prior to hepatic or pancreatic surgery are associated with an increased rate of bacterial biliary contamination. Therefore, infectious complications are described more frequently in these patients [27,28]. Unfortunately, due to the small patient sample without prior endoscopic procedures in this study, the comparison between patients with and without endoscopy could not undergo valid statistical analysis.

The risk of developing intrahepatic cholangiocarcinoma is increased by 100-fold in patients with CD/CS [29]. Furthermore, it is difficult to detect a tumor within the dilated biliary tract, making early detection almost impossible. The tumor is often detected in the final pathology examination of the surgical specimen [29]. In addition, in this study, tumor markers such as Ca 19-9 often failed to detect cancer or were even found to be elevated without cancer due to local cholestasis with hyperbilirubinemia, factors that have been previously shown to affect Ca 19-9 levels [30]. One explanation for tumor development is a long-standing chronic inflammation and injury to the biliary epithelium, progressing to dysplasia and epithelial carcinogenesis [22]. It has been speculated that the risk of developing cancer is higher in cases of dilatation of the large bile ducts than in patients with a dilatation of the peripheral ducts [12]. In our study, the incidence of cholangiocarcinoma was 21%, which is higher than the 14% reported in previously published studies [3,7,11,12]. Patients were transferred to the hepatobiliary unit at our center after ineffective treatment in low-volume hospitals. Delayed curative treatment might promote tumor development. This highlights the fact that early and stage-dependent curative treatment may be necessary in order to offer these patients an adequate therapy with acceptable long-term survival and good quality of life.

In the United States, the reported case rate of LTX for CD averaged six patients annually during the years 1989 to 2011 [31]. Several studies dealing with liver transplantation in patients with the diffuse type of CD and CS have shown favorable results [11,15,32,33]. As shown in the UNOS/OPTN database of LTX for CD, the survival rates are comparable or even better compared to other diseases undergoing LTX [31]. Habib et al. demonstrated that patients with CS or active cholangitis at the time of LTX had reduced survival in comparison to patients with CD and without cholangitis [7]. Thus, if possible, LTX should be performed in patients without acute cholangitis and not during a septic episode. In addition, pre-operative antibiotic prophylaxis should include the already known bacterial spectrum. Therefore, when the option of performing living donor liver transplantation is available, transplantation might be postponed to a later time point without acute inflammation. In 2010, Hori et al. presented a series of eleven LTX in patients with congenital biliary dilatation, of whom ten patients obtained living donor liver transplantations with a ten-year survival rate of 90% [17]. Due to their lower priority on the waiting list for LTX, patients with CD might benefit from living-donor liver transplantations with consequently shorter waiting times and a lower risk of life-threatening complications [14]. Living-donor liver transplantation is a technically demanding, but feasible technique. In our opinion, in view of the limited availability of donor organs, it could be proposed for patients with CD requiring LTX [34]. The incidence of biliary stricture after living donor liver transplantation, as was seen in one patient included in this study, has been reported in many series, with a rate up to 27%, but may often be successfully treated with interventional procedures [17,35].

The retrospective nature of the study design has potential limitations, which should be taken into account, as specific information may be lacking from patient records. In addition, five years of follow-up is likely not sufficient to detect disease recurrence or tumor recurrence or to assess long-term survival.

Conclusion

In conclusion, this study underlines the role of hepatic resection in CD or CS, which can be performed with acceptable morbidity and low mortality. In case of bilobar disease and liver cirrhosis, LTX is a valuable therapeutic option with excellent long-term results. Overall, the incidence of liver resection and liver transplantation for this entity is rare. As the risks of cholangiocarcinoma and septic complications increase over time with CD and CS, liver resection or transplantation should be performed as early as possible.

Disclosure of interest

The authors S.G.C.D., M.A. and U.S. declare that they have no competing interest.

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