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ORIGINAL ARTICLE

The place of liver transplantation in Caroli's disease and syndrome

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Summary

Caroli's disease (CD) or syndrome (CS) are rare inherited disorders which may cause severe, life-threatening, cholangitis or which may lead to hepatobiliary degeneration. The typical cystic biliary anomalies are often associated to congenital hepatic fibrosis (CHF) and, less frequently, to cystic renal disease especially autosomic recessive polycystic kidney disease (ARPKD). The place of liver transplantation (LT) in the treatment of CD or CS is evaluated based on our own experience of three successfully transplanted patients, the literature review of 19 patients and the European experience with 110 patients collected in the European Liver Transplant Registry. LT should be proposed as a definitive therapeutic option once severe cholangitis or (suspicion of) malignant transformation is present. The frequently used radiological, endoscopical or surgical biliary drainage procedures carry a high morbidity and mortality rate. In case of concomitant symptomatic CHF and renal failure, combined or sequential hepatorenal transplantation should be carried out, dependant on the evolution of the hepatic and renal disease. In case of associated ARPKD, renal transplantation is often indicated early on because of the more rapid progression of the renal component of the disease.

Introduction

Caroli's disease (CD) is a rare, mostly autosomal recessive, inherited disorder characterized by macroscopic, mostly mutifocal, saccular or segmental ectasias of the intrahepatic bile ducts [1]. It is frequently associated to congenital hepatic fibrosis (CHF) and to autosomic recessive polycystic kidney disease (ARPKD) [2–5]. The latter combination is caused by mutations in Polyaptic Kidney Hepatic Disease 1 (PKHD1) [6]. The term Caroli syndrome (CS) covers the whole spectrum of the disease.

The evolution of CD or CS is dominated by the occurrence of repetitive bouts of cholangitis, the frequency of which may vary importantly from one patient to another. In case of frequent episodes of cholangitis, the long-term prognosis is dismal. CD or CS can be complicated by the formation of liver abscesses, intra- and extrahepatic lithiasis and even cholangiocarcinoma (CHCA) [6].

As the presentation and evolution of CD or CS is very variable, the value of liver transplantation (LT) in the treatment of this condition is not well standardized. This study evaluates the place of LT in the treatment of this rare disorder.

Material and method

During the period 1987–2004, three patients were transplanted for this indication in our liver transplant center. The literature relating to 19 patients and the experience collected by the European Liver Transplant Registry (ELTR) with 110 patients are also reviewed.

Patient 1

A 11-year-old Italian girl, having ARPKD, presented (in 1986) several episodes of cholangitis and bleeding because of ruptured esophageal varices. She as well as her brother (case 3) presented PKHD1 mutation; her sister and parents were disease-free. At examination, this teenager presented in a poor general condition with pronounced growth retardation (<p3), collateral venous circulation, and extreme abdominal organomegaly. CT-scan, ultrasound, and transcutaneous cholangiography revealed hepatosplenorenomegaly, inverted portal flow, and multiple intrahepatic biliary cystic dilations. Liver biopsy confirmed the diagnoses of CHF and acute cholangitis. Because of the presence of symptomatic liver cirrhosis and of end-stage renal failure, combined hepatorenal transplantation was performed in 1987, using organs from the same post-mortem donor (Fig. 1). Left nephrectomy was carried out to enlarge abdominal cavity. Immunosuppression (IS) consisted of R-ATG (Fresenius, Homburg, Germany), cyclosporine (CyA) (Neoral®, Novartis, Basel, Switzerland) and steroids. Except for a convulsive episode, the early post-transplant evolution was uneventful. Five years later acute renal rejection needed treatment with steroid boluses. In 1993, HCV-Ab serology became positive. In 1999, she was switched to tacrolimus (TAC) (Prograft®, Fujisawa, Osaka, Japan). In 2001, liver biopsy showed moderate chronic HCV hepatitis. Because of the fear for renal rejection, no antiviral treatment was given. Nineteen years after transplantation, she is asymptomatic having normal Doppler-ultrasound examinations as well as normal liver and renal tests.

Patient 2

A 61-year-old male was diagnosed in 1990 to have diffuse CD, when presenting a first episode of biliary pancreatitis. In 1995, a second episode of cholangitis was treated using endoscopic choledochal stone removal. In the two following years, he had several serious episodes of cholangitis, resulting finally in 1997 in life-threatening septic shock and acute renal failure. Bile cultures showed polymicrobial infection (*Pseudomonas aeruginosa, Proteus vulgaris, Escherichia coli, Enterococcus faecalis*). Cholangio-MNR confirmed a diffuse bilobar intrahepatic lithiasis in the context of CD (Fig. 2). LT was performed at age of 68 years using TAC and low-dose short-term steroid IS. At post-LT day 30, humoral rejection led to massive hemorrhagic necrosis of a blood group identical allograft. Crossmatch at moment of LT was negative. He was successfully retransplanted (reLT) at day 43. Fourteen days after reLT steroid, boluses were necessary to treat acute rejection. After 8 years post-LT, he is doing extremely well under low-dose TAC monotherapy.

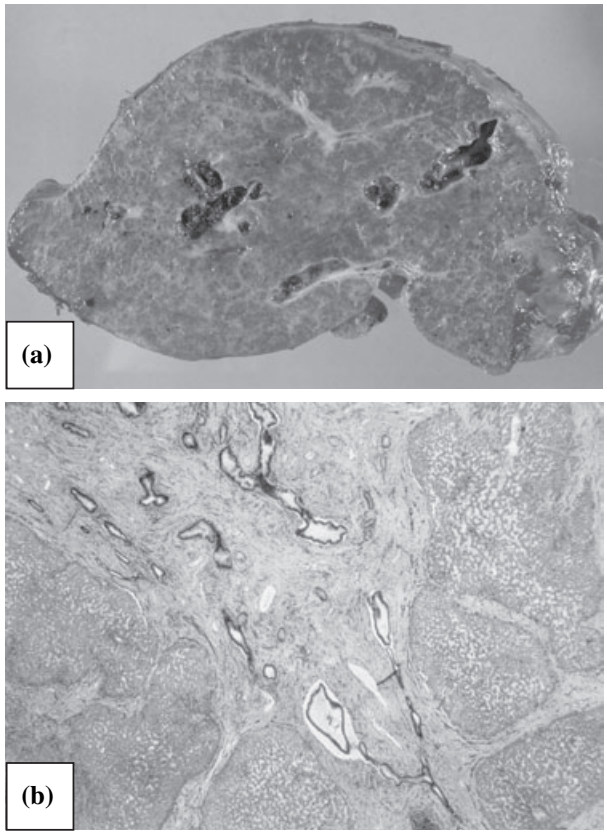

Figure 1 Caroli's syndrome. (a) Native hepatic resection specimen (patient 1): section of liver showing fine reticular pattern of fibrosis. Some cystically dilated bile ducts are observed. Their lumen contains inspissated bile or soft and friable bilirubin calculi. (b) Histology of native hepatic parenchyma (patient 1), demonstrating typical jigsaw pattern, as a result of diffuse periportal fibrosis. Fibrous tissue includes small scattered and irregularly shaped bile ducts, some of which are slightly dilated and contain bile (hematoxylin-eosin, low-power magnification).

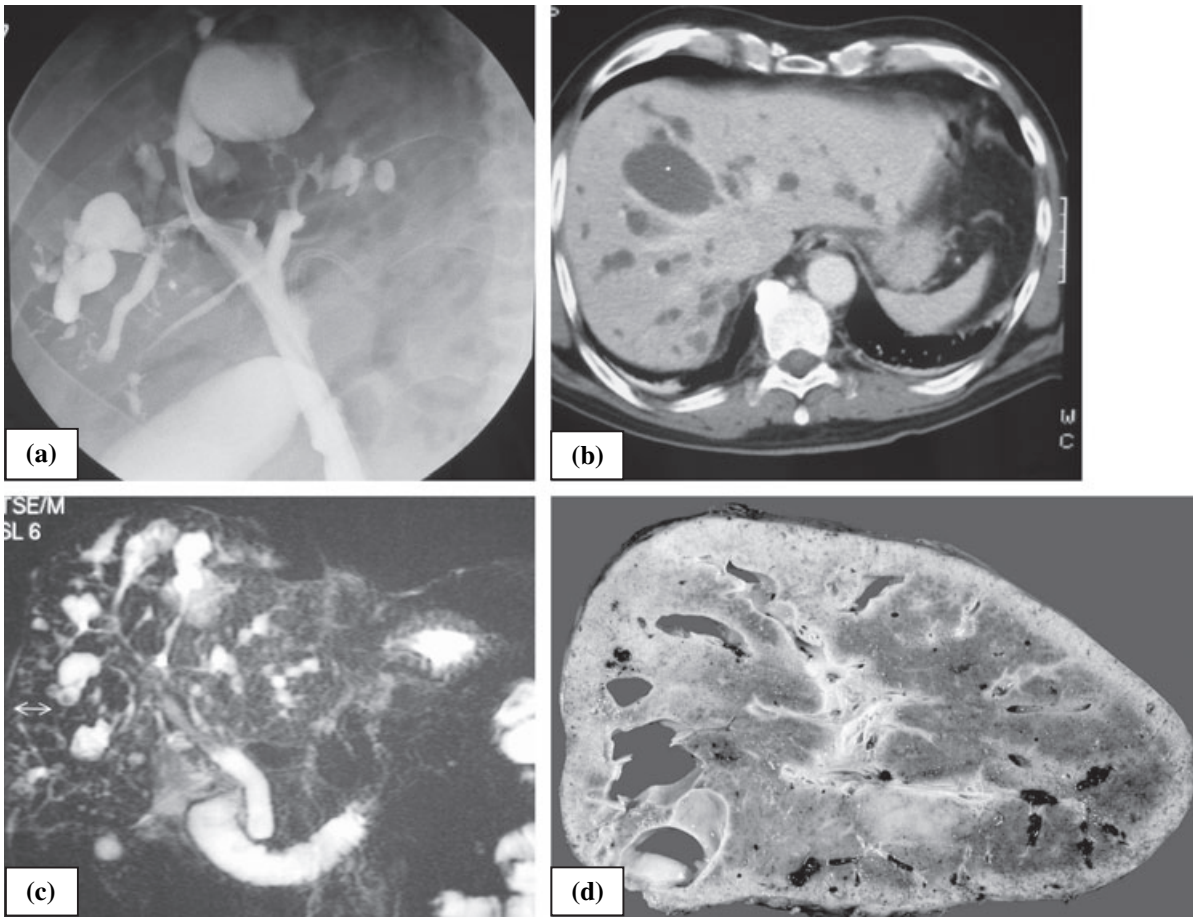

Figure 2 Typical findings of Caroli's disease (CD) at (a) endoscopic retrograde cholangiography, (b) computed tomography, (c) cholangio-MNResonance imaging and (d) histology. The section of the native liver section shows intrahepatic cystic dilations, some of them with bilirubin calculi in their lumen (patient 2).

Patient 3

Autosomic recessive polycystic kidney disease (ARPKD) was diagnosed at the age of 4 months in the older brother of our first patient. He also presented the PKHD1 mutation. At age of 15 years, chronic hemodialysis became necessary because of end-stage renal failure. When he was referred 2 years later for renal transplantation (RTr), he had no hepatobiliary disease diagnosed. Four years later, RTr was performed under CyA and steroid IS. Three episodes of acute rejection lead to chronic allograft dysfunction. At the age of 27 years, symptomatic portal hypertension, because of CHF, was diagnosed. Surgical portocaval shunting was necessary to control bleeding esophageal varices. At that time, HCV-Abs were positive. Following several episodes of cholangitis, the diagnosis of CS was made at the age of 29 years. At that time, he refused the proposed LT. Despite long-term antibiotherapy, several episodes of cholangitis occurred resulting finally in 2004 in a life-threatening septic shock with acute renal failure. Blood cultures were positive for multiresistant *E. coli*. Cholangio-MNR confirmed bilobar cystic biliary dilations containing multiple stones. Calculated creatinin clearance (Cockroft) remained stable around 30 ml/min/1.73m^2. In July 2004, at the age of 36 years, combined hepatorenal transplantation was performed. Immunosupression consisted of TAC, steroid, and mycophenolate mofetil (Cellcept®; Roche, Basel, Switzerland). The postoperative period was marked by a wound abscess and aggravation of pre-existing right leg distal arteritis, leading to femoral angioplasty and to lower limb amputation. After eighteen months post-LT, he is doing well under triple immunosuppression, having normal renal and liver functions.

Literature review

Nineteen patients, transplanted because of CD or CS, have been reported in literature [7–18] (Table 1). Median

Table 1. Liver transplant literature in relation to Caroli's disease (CD) or syndrome.

Author	Refs.	Year	*n*	Age at LT	Sex	Associated diagnosis	PHT	Pre-LT treatment	Complication post-treatment	Indication LT	Duration sympt. (years)	Associated renal transpl.	Biliary reconstr.	Complication post-LT	Follow-Up (months)	FU graft function
Balsells	[12]	1993	1	25	F			Exploratory laparotomy		CHCa-rec chola	14		RY-HJ	Acute rejection	24	Normal
Sans	[9]	1997	2	64	F			RY-HJ	Cholangitis	Rec chola	2		RY-HJ	HCV-Chronic Hep. Acute rejection 1.5 years	60	Good
				21	M			Exploratory laparotomy		Rec chola	14			Wound infection d9 acute rejection d21	8	Normal
Schiano	[13]	1997	1	35	F	CHF	No	Diagnostic ERC	Biliary sepsis: pancreatitis	Rec chola	4		RY-HJ	HAT d1 > revision acute necrotic pancreatitis d2 acute rejection d70	21	Normal
Marx	[10]	1999	1	24	F	ARPKD				Rec chola	NA	Previous (2×) simultaneous	NA	HAT > reLT	3	Normal
Waechter	[16]	2001	2	41	M	CHF		–		Rec chola	3		NA	Acute rejection 3 months	NA	Normal
				32	M	CHF		Left hepatectomy-RY-HJ		Rec chola	1		NA		NA	Normal
Takatsuki	[8]	2001	1	37	F			–		Papillary adenoca-rec chola	1		(LDLT)		29	Normal
Ninan	[11]	2002	1	25	F	ARPKD		Endoscopic sphincterotomy	Biliary sepsis	Rec chola	5	Previous			48	Normal
Ammori	[7]	2002	6			NA		Partial liver resection	Recurrent Caroli	SBC-rec chola	> 9		RY-HJ	Unknown CHCa	16 dead	Rec CHCa
						NA		Partial liver resection	Recurrent Caroli	SBC-rec chola	> 2		RY-HJ	NA		?
				35 (23–55)	4F/2M	NA	Yes	NA		SBC-rec chola	NA		RY-HJ	NA	20(15–32)	?
						NA	Yes	NA		SBC-rec chola	NA		RY-HJ	NA		?
						ARPKD	yes	NA		SBC-rec chola	NA	Previous	RY-HJ	NA		?
						MSKD	Yes	NA		Multiple localizations CHCA-rec chola	NA	Simultaneous	RY-HJ	NA	3 dead	Rec CHCa
Ulrich	[6]	2002	4	43	M	CHF	Yes	Endoscopic procedures		Rec chola	12		NA	Acute rejection d7	84	Normal

		30	F			Endoscopic procedures right lobectomy-RY-HJ		Rec chola	9		NA	Acute reject. 1–2 years	NA	Good
		44	F			Endoscopic procedures left hepatectomy	HCV-infection	Rec chola	13		NA	HCV-chronic hep.	36	Normal
		61	M	AML		Cholecystectomy endoscopic procedures		Rec chola	29	Simultaneous	NA		5	Good
UCL	2005	3	11	F	CHF / ARPKD	Yes	Diagnostic PTC		Rec chola	1	Simultaneous	DD	HCV-Chronic Hep	204	Good
			68.1	M			ERC drainage and stone removal	Biliary sepsis	Rec chola	7		DD	Acute rej d30>reLT	84	Normal
			36	M	CHF /ARPKD	Yes	Portocaval shunt		Rec chola	7	Previous simultaneous	DD	HCV-Chronic Hep	8	Normal
Total		22	36 (11–68,1)	13F 9M	6 (27.3%) Renal disease 6 (27.3%) CHF				4 CHCa (18.1%)	12 (1–29)	7 (31.8%)			48 (3–204)	

CHF, congenital hepatic fibrosis; ARPKD, autosomic recessive polycystic kidney disease; MSKD, medullary sponge kidney disease; AML, amyloidosis; PHT, portal hypertension; SBC, secondary biliary cirrhosis; LDLT, living donor LT; Rec chola, recurrent cholangitis; CHCA, cholangiocarcinoma; RY-HJ: Roux-Y hepatico-jejunostomy; DD, duct-to-duct anastomosis; NA, not available.

age at LT of our three patients and of the 19 reported patients was 36 years (range 11–68.1). Median delay between diagnosis and LT was 12 years (range 1–29). Half of the patients underwent one or more endoscopic (six patients) or surgical biliary (eight patients) drainages before LT. Bilio-enteric anastomosis was carried out in three patients and five patients had partial liver resection.

Diagnosis of CS was confirmed in all patients before LT. Associated findings of CS were: CHF in six (27.3%) patients, ARPKD in four (18.2%) patients, medullar sponge kidney disease in one (4.5%), and amyloïdosis in one (4.5%) patient. All patients had presented recurrent cholangitis either spontaneously or induced by invasive biliary tract exploration.

The primary indications for LT were cholangitis in 20 (90.9%) patients and malignant degeneration in two (9.1%) patients.

Seven (31.5%) patients had a hepatorenal transplantation. Three (13.6%) patients had previous RTr because of ARPKD and five (22.7%) patients had simultaneous hepatorenal transplantation. Right lobe living donor LT was carried out once. After post-LT, one (4.5%) patient needed revision for hepatic artery thrombosis and two (9%) patients had successful reLT because of hepatic artery thrombosis and because of humoral graft rejection.

Histological examination of the hepatectomy specimen revealed CHCA in four (18.2%) patients. Both patients, in which this cancer was unknown, died of tumor recurrence after 3 and 16 months LT; both patients, in which the cancer was known before LT, were reported alive 2 years after LT. All survivors have good allograft function without any recurrence of cholangitis after a median follow-up, available in 19 (90.5%) of the 22 patients, of 48 months (3–204).

ELTR data

During the period 1968–2003, 110 patients underwent LT because of CD or syndrome in Europe. There were 57 males and 53 females with a median age of 39.7 years (range 0.4–68.1). Associated diseases were under-reported as only mentioned in eight (7.8%) patients : polycystic renal disease (three patients), CHF (two patients, 1.8%) and CHCA (three patients, 2.7%). Fifty-one (46.4%) patients were under continuous medical care at moment of LT (Unos 1: five patients; Unos 2: 11 patients; Unos 3: 35 patients) because of, mainly septic, complications of their disease. Four (3,6%) patients were transplanted urgently.

Although only three associated renal diseases were reported, sixteen (14.5%) patients had simultaneous hepatorenal transplantation.

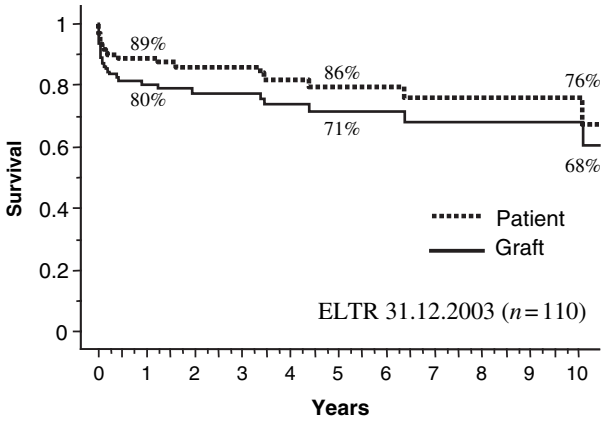

Figure 3 Five year actuarial patient and graft survival rates after liver transplantation performed for CD or syndrome: ELTR data in 110 patients transplanted between 1968 and 2003.

After a median follow-up of 812 days (range 0–6083 days), 89 patients are alive. Fifteen (13.6%) patients needed a re-LT because of vascular thrombosis (eight patients), primary graft nonfunction (two patients), acute rejection (two patients) and because of unspecified reason (three patients); seven of these patients died. One of three tumor patients died at post-LT day 152 because of early tumor recurrence; the two other tumor patients are reported alive after 15 and 1.5 years, respectively.

Only one (4.7%) of 21 patients died after LT because of a bacterial infection.

Five-year actuarial patient and graft survival rates were 76% and 68%, respectively (Fig. 3).

Discussion

Caroli disease is a rare, mostly autosomal recessive inherited, congenital disorder, characterized by macroscopic saccular or segmental ectasias of the intrahepatic bile ducts [1]. This disease is frequently associated to CHF. The common etiology of these fibrocystic diseases is probably related to ductal plate malformation at different levels of the intrahepatic biliary tree: large bile ducts for CD and small ducts for CHF, respectively [2]. The liver involvement can be segmental or diffuse. The degree of periportal fibrosis and of intrahepatic bile duct dilation is highly variable, so that the entire spectrum from CD to CHF with secondary cirrhosis may be encountered. The term CS is used to cover the whole spectrum of the disease. The renal involvement, associated in up to 60% to CS, implies a dilation of the collecting renal tubules [3–5]. The association between CHF and ARPKD is caused by mutations in PKHD1 that encodes fibrocystin, a protein of primary cilia. Genetic defects in fibrocystin cause ciliary dysfunction, presently considered as a major pathogenic event in cystogenesis [6].

Clinical progression and presentation of CS is highly variable and symptoms may appear early or late during life. Bile stagnation and hepatolithiasis explain the recurrent cholangitis, which dominates the clinical course and which is the principal cause of morbidity and mortality. Chronic abdominal pain, pancreatitis, and liver abscess are other disease manifestations. Some patients with rapidly progressing CHF may present portal hypertension before or at the same time of the onset of biliary symptoms. In the majority of patients, portal hypertension will not be present or will appear only later on in the disease evolution. In such situation, minimal CHF may be detected in the explanted liver. It should be stressed that CHF does not lead to liver insufficiency.

The risk of hepatobiliary malignant transformation, explained by chronic inflammation of the biliary tree, has been reported in 7–14% of patients with CS [19–21]. Medical treatment of CS using ursodeoxycholic acid and antibiotherapy may stabilize the disease [22]. Emergence of polymicrobial flora, resistance to antibiotics and persistence of germs encapsulated in lithiasis decrease however efficiency of anti-infectious therapy and make therapy of enfollowing sepsis even hazardous [11]. Invasive biliary tract *diagnostic* procedures should be avoided as they may be responsible for intractable biliary sepsis. Cholangio-MNR nowadays allows to make the correct diagnosis without endangering the patient's life. In case of presence of cholangitis caused by impacted stones or dominant strictrure nonsurgical interventions may be very useful to overcome septic episodes.

Interventional radiological, endoscopical and surgical biliary drainage procedures are, however, palliative treatments that may improve (temporarily) bile drainage but that become finally inefficient in relation to disease progression. Numerous nonsurgical procedures have not only a poor long-term efficiency, but they also may worsen the infectious situation. Bilioenteric anastomosis, with or without partial hepatectomy, carries a high, infectious morbidity [10,23–26]. Cholangitis occurs after a technically satisfactory biliary drainage, because of impaired functional or morphological jejunal limb motility, bacterial translocation to the liver through the splanchnic venous or lymphatic systems, impaired hepatic lymph drainage, and ascending infection from the jejunal limb [27,28]. Spectroscopy is indeed able to show reflux in any organ situated above a correctly constructed Roux-Y limb [29]. This condition is particularly important in case of immunosuppression (related to a previous RTr in these patients) [30]. Hepatic resection is the treatment of choice in case of monolobar forms of the disease, in absence of CHF, as very good long-term results can be

offered [8,31–36]. One should, however, be aware that disease progression has been reported after partial resection because of further development of residual disease in the remnant liver [8,37].

This review confirms that LT is a curative therapy for CD or CS with an acceptable morbidity. Recently, living-related donor LT has also been introduced successfully in the treatment of CD with apparently no unfavorable effects for recipient nor donor [8]. Both the reported experience and the knowledge of disease history indicate that LT should be proposed to patients presenting with recurrent cholangitis, especially in the context of diffuse type of CD. Indication for LT should be put forward timely as these patients usually do not present with an end-stage liver failure, which implicates usually a waiting time within Europe of (6 to) 12 months. Multidisciplinary approach of these patients is therefore of utmost importance. Repeated palliative treatments should be avoided because of the prolongation of the symptomatic period and the increased risk of malignant transformation [8,34].

The congenital fibropolycystic diseases of the biliary system are associated with increased risks of CHCA [38]. The diagnosis of CHCA in this setting is, however, difficult as there are apparently no clear clinical nor biochemical parameters allowing to make an early cancer diagnosis, a condition similar to that encountered in primary sclerosing cholargiks (PSC) [39,40]. There is also no clear timeline known in relation to malignant degeneration; indeed, CHCA has been reported up to 23 years after careful follow-up of CD [41]. A localized biliary tumor may represent a valid indication for LT although no long-term follow-up is available in the reported cases; advanced CHCA remains a contraindication to LT in view of the poor long-term results [8,12]. The disappointing Canadian results obtained in case of LT for incidental CHCA, developed in the context of PSC, needs to be kept in mind when selecting a patient with CD and known CHCA for such a treatment[42]. Improvement of liver transplant results for CHCA in general seems only possible in case of neo-adjuvant chemoradiation-therapy. It is unlikely that these measures will be applicable to CD with CHCA, as more than 90% of transplant indications are related to prolonged biliary infection [43].

In case of associated renal disease, end-stage renal failure usually occurs during childhood, before the onset of CD. It has been suggested that the immunosuppressed status of the kidney transplanted patient may contribute to the later development of cholangitis[11,12]. If renal and hepatobiliary disease progress concomitantly, simultaneous hepatorenal transplantation is indicated.

Liver transplantation represents the only curative treatment for diffuse symptomatic CD or CS. LT should be offered early in case of recurrent cholangitis and (suspicion of) early malignant transformation of the biliary tract. In case of associated renal disease, both renal and liver diseases should be documented regularly and precisely in order to optimize the decision to perform sequential or combined hepatorenal transplantation.

References

1. Caroli J, Soupault R, Kossakowski J, Plocker L, Paradowska M. Congenital polycystic dilation of the intrahepatic bile ducts; attempt at classification. *Sem Hop* 1958; **34**: 488.
2. Desmet VJ. Ludwig symposium on biliary disorders – part I. Pathogenesis of ductal plate abnormalities. *Mayo Clin Proc* 1998; **73**: 80.
3. Waters K, Howman-Giles R, Rossleigh M, Lam A, Uren R, Knight J. Intrahepatic bile duct dilatation and cholestasis in autosomal recessive polycystic kidney disease. Demonstration with hepatobiliary scintigraphy. *Clin Nucl Med* 1995; **20**: 892.
4. Nakanuma Y, Terada T, Ohta G, Kurachi M, Matsubara F. Caroli's disease in congenital hepatic fibrosis and infantile polycystic disease. *Liver* 1982; **2**: 346.
5. Zerres K. Autosomal recessive polycystic kidney disease. *Clin Investig* 1992; **70**: 794.
6. Housset C. Cystic liver diseases. Genetics and cell biology. *Clin Biol* 2005; **29**: 861.
7. Ulrich F, Steinmuller T, Settmacher U, *et al.* Therapy of Caroli's disease by orthotopic liver transplantation. *Transplant Proc* 2002; **34**: 2279.
8. Ammori BJ, Jenkins BL, Lim, et al. Surgical strategy for cystic diseases of the liver in a western hepatobiliary center. *World J Surg* 2002; **26**: 462.
9. Takatsuki M, Uemoto S, Inomata, *et al.* Living-donor liver transplantation for Caroli's disease with intrahepatic adenocarcinoma. *J Hepatobiliary Pancreat Surg* 2001; **8**: 284.
10. Sans M, Rimola A, Navasa M, *et al.* Liver transplantation in patients with Caroli's disease and recurrent cholangitis. *Transpl Int* 1997; **10**: 241.
11. Marx G, Nashan B, Cobas Meyer M, *et al.* Septic shock after liver transplantation for Caroli's disease: clinical improvement after treatment with C1-esterase inhibitor. *Intensive Care Med* 1999; **25**: 1017.
12. Ninan VT, Nampoory MR, Johny KV, *et al.* Caroli's disease of the liver in a renal transplant recipient. *Nephrol Dial Transplant* 2002; **17**: 1113.
13. Balsells J, Margarit C, Murio E, *et al.* Adenocarcinoma in Caroli's disease treated by liver transplantation. *HPB Surg* 1993; **7**: 81.
14. Schiano TD, Fiel MI, Miller CM, Bodenheimer HC Jr, Min AD. Adult presentation of Caroli's syndrome treated with orthotopic liver transplantation. *Am J Gastroenterol* 1997; **92**: 1938.

15. Garcia Valriberas R, Diaz Blasco J, Moreno Monteagudo JA, Correa JA, Garcia Buey ML, Pajares Garcia JM. Acute pancreatitis in Caroli's syndrome. *Rev Esp Enferm Dig* 1997; **89**: 133.
16. Tommaso de AM, Santos DS, Hessel G. Caroli's disease: 6 case studies. *Acta Gastroenterol Latinoam* 2003; **33**: 47.
17. Waechter FL, Sampaio JA, Pinto, *et al.* The role of liver transplantation in patients with Caroli's disease. *Hepatogastroenterology* 2001; **48**: 672.
18. Harjai MM, Bal RK. Caroli syndrome. *Pediatr Surg Int* 2000; **16**: 431.
19. Dayton MT, Longmire Jr WP, Tompkins RK. Caroli's disease: a premalignant condition? *Am J Surg* 1983; **145**: 41.
20. Phinney PR, Austin GE, Kadell BM.Cholangiocarcinoma arising in Caroli's disease. *Arch Pathol Lab Med* 1981; **105**: 194.
21. Chapman RW. Risk factors for biliary tract carcinogenesis. *Ann Oncol* 1999; **10 S4**: 308.
22. Ros E, Navarro S, Bru C, Gilabert R, Bianchi L, Bruguera M. Ursodeoxycholic acid treatment of primary hepatolithiasis in Caroli's syndrome. *Lancet* 1993; **14**: 404.
23. Witlin LT, Gadacz TR, Zuidema GD, Kridelbaugh WW. Transhepatic decompression of the biliary tree in Caroli's disease. *Surgery* 1982; **91**: 205.
24. Merono-Cabajosa EA, Celdran-Uriarte A, Moreno-Caparros A, Solera-Arroyo JC, Marijuan-Martin JL. Caroli's disease: study of six cases, including one with epithelial dysplasia. *Int Surg* 1993; **78**: 46.
25. Benhamou JP. Congenital hepatic fibrosis and Caroli's disease. In: Schiff L, Schiff ER, eds. *Diseases of the Liver*, 6th edn. Philadelphia: Lippincott, 1987: 820–823.
26. Nagasue N. Successful treatment of Caroli's disease by hepatic resection. Report of six patients. *Ann Surg* 1984; **200**: 718.
27. Orlando G, Blairvacq JS, Otte JB, *et al.* Successful treatment of recurrent cholangitis after adult liver transplantation with a Tsuchida antireflux valve. *Transplantation* 2004; **77**: 1307.
28. Collard JM, Romagnoli R. Roux-en-Y jejunal loop and bile reflux. *Am J Surg* 2000; **179**: 298.
29. Chuang JH, Lee SY, Chen WJ, *et al.* Changes in bacterial concentration in the liver correlate with that in the hepatico-jejunostomy after bile duct reconstruction: implication in the pathogenesis of postoperative cholangitis. *World J Surg* 2001; **25**: 1512.
30. Chuang JH, Chen WJ, Lee SY, *et al.* Prompt colonisation in the hepatico-jejunostomy and translocation of bacteria to liver after bile duct reconstruction. *J Pediatr Surg* 1998; **33**: 1215.
31. Knoop M, Keck H, Langrehr JM, Peter FJ, Ferslev B, Neuhaus P. Therapy of unilobar Caroli syndrome by liver resection. *Chirurg* 1994; **65**: 861.
32. Gillet M, Favre S, Fontolliet C, Halkic N, Mantion G, Heyd B. Monolobar Caroli's disease. A propos of 12 cases. *Chirurg* 1999; **124**: 13.
33. Madariaga JR, Iwatsuki S, Starzl TE, Todo S, Selby R, Zetti G. Hepatic resection for cystic lesions of the liver. *Ann Surg* 1993; **218**: 610.
34. Moreno GE, Gomez SR, Hidalgo PM, Garcia GI, Rico SP, Calle SA. Surgical treatment of congenital dilatation of the biliary system. *Hepatogastroenterology* 1993; **40**: 134.
35. Kassahun WT, Kahn T, Wittekind, *et al.* Caroli's disease: liver resection and liver transplantation. Experience in 33 patients. *Surgery* 2005; **138**: 888.
36. Benhidjeb T, Muller JM, Gellert K, Zanow J, Rudolph B. Current therapy of bile duct cysts. Intrahepatic cysts, Carolisyndrome. *Chirurg* 1996; **67**: 238.
37. Izawa K, Tanaka K, Furui J, *et al.* Extended right lobectomy for Caroli's disease: report of a case and review of hepatectomized cases in Japan. *Surg Today* 1993; **23**: 649.
38. Chapman RW. Risk factors for biliary tract carcinogenesis. *Ann Oncol* 1999; **10 S4**: 308.
39. Abdalla EK, Forsmark CE, Lauwers GY, Vauthey JN. Monolobar Caroli's disease and cholangiocarcinoma. *HPB Surg* 1999; **11**: 271.
40. Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ Jr, LaRusso NF. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg* 1991; **213**: 21.
41. Ridwelski K, Benhidjeb T, Wolff H, Munster B, Schulz HJ. Diagnosis and surgical therapy in congenital ectasias of the intra- and extrahepatic bile ducts. *Zentralbl Chir* 1991; **116**: 1159.
42. Ghali P, Marotta PJ, Yoshida EM, *et al.* Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. *Liver Transpl* 2005; **11**: 1412.
43. Heimbach JK, Rosen CB, Haddock MG, *et al.* Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; **242**: 451.