Treatment of Highly Symptomatic Polycystic Liver Disease

Preliminary Experience with a Combined Hepatic Resection–Fenestration Procedure

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Polycystic liver disease (PLD) associated with autosomal dominant polycystic kidney disease is usually well tolerated. However there is a small subset of patients who become incapacitated by massive liver enlargement and for whom effective nonsurgical therapy is limited. Recent surgical advances in the treatment of PLD have raised uncertainties regarding proper management of these highly symptomatic patients. We have reviewed our recent experience with a combined hepatic resection–fenestration procedure to assess its efficacy in nine patients. All patients underwent resection of two or more liver segments and extensive fenestration of residual cysts in the remnant liver. Symptomatic relief and reduction in abdominal girth were obtained in eight surviving patients, persisting for an average follow-up period of 17 months. No progression of cystic disease has been observed clinically or by computed tomography and hepatic function was preserved. Three patients had no complications. Five patients had complications including transient right pleural effusion (3) and thrombosis of an arteriovenous fistula (2). One patient who had a previous hepatic cyst fenestration and a cadaveric renal transplantation died after operation of an intracerebral hemorrhage after experiencing coagulopathy, hyperbilirubinemia, and sepsis. Our results suggest (1) some highly symptomatic patients with massive PLD may benefit from combined hepatic resection and fenestration with acceptable risk, and (2) previous liver surgery and immunosuppressive therapy may increase the risk of such surgery. Longer follow-up is needed in a larger number of patients to determine the duration of benefit from the combined resection–fenestration procedure for highly symptomatic PLD.

MULTIPLE HEPATIC CYSTS or polycystic liver disease (PLD) are frequently associated with autosomal dominant polycystic kidney disease (ADPKD).[1–5] During the past three decades, medical advances have increased the number of patients with ADPKD who survive long enough to develop severe liver involvement. As experience with such patients has increased, so too has the uncertainty over their proper management. Not infrequently symptomatic patients with PLD exhaust all conservative therapeutic options and surgery is considered the next alternative. Our purpose was to determine the value and consequences of combined hepatic resection and cyst fenestration for highly symptomatic patients with polycystic liver disease from our recent experience.

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Accepted for publication October 2, 1989.

Patients and Methods

We reviewed the medical records of all patients with ADPKD who underwent radical resection for highly symptomatic PLD at the Mayo Clinic from 1985 to 1989. All patients were operated on by a single surgeon (DMN). Information abstracted from patient records included selection criteria, operative technique and extent of surgery, postoperative course, complications, and follow-up.

Patients were selected primarily on the basis of the severity of abdominal symptoms and impairment of clinical performance as estimated by the Performance Status Scale of the American Cancer Society Eastern Cooperative Oncology Group (ECOG). A score of 0 was assigned to unrestricted patients, 1 to patients restricted from strenuous physical activity, 2 to patients capable of self care, 3 to confined patients, and 4 to invalid patients.[6] Additional indications for operation included infection of one or more hepatic cysts refractory to antibiotics and to percutaneous drainage, regardless of performance status. Hematology, coagulation and chemistry profiles, and nutritional assessment were obtained in each patient. Abdominal computed tomography (CT) scan was performed to delineate cyst distribution, to assess portal vein patency, and to serve as a baseline for follow-up comparison. In addition six patients had an exercise radionuclide cineangiography or a dipyridamole-thallium study to assess cardiovascular performance. Seven patients also had

evaluation of their cerebral vasculature either by high-resolution computed tompgraphy (CT) scanning or by magnetic resonance imaging (MRI) to detect aneurysmal disease.[7] If no major medical contraindication to resection was identified, specific hepatic factors were evaluated. Only patients with no major abnormalities of hepatic function tests, a patent portal vein, and relative sparing of two or more adjacent liver segments underwent resection.

Preoperative preparation of each patient included an overnight lavage bowel preparation with oral antibiotics, central venous catheterization, and dialysis or intravenous hydration as indicated. The abdomen was explored through a bilateral subcostal incision. Ascitic fluid was collected, if present, for culture and analysis. The liver was mobilized by division of its peritoneal attachments. The hepatoduodenal ligament was exposed to provide maximal access for vascular inflow occlusion and identification of major vascular and biliary structures. Liver segments spared of cystic involvement were identified before parenchymal transection to define limits to resection. Liver parenchyma and cysts were divided without ligation of hilar vessels or hepatic veins. In fact these structures were often inaccessible to ligation due to liver enlargement. Parenchyma was transected by a modification of the Lin technique with sequential fenestration of cysts along the projected transection plane between diffusely cystic and spared liver.[8] Using cautery, the transection plane is developed further by division and excision of intercystic septa.[9] Vascular and biliary radicles that coursed through the cyst septae were suture ligated as indicated. Precise transection through anatomic segmental or lobar planes was precluded due to cystic distortion of normal anatomy. Significant islands of functional liver parenchyma were preserved. After resection of major cystic segments, extensive fenestration of residual cysts was performed by excision of the cyst walls. Finally cyst cavities exposed to the peritoneum were fulgurated by electrocautery or by argon beam coagulation (Bard Electromedical Systems, Englewood, CO) in an attempt to ablate secretory epithelium and reduce postoperative peritoneal fluid losses. Cholecystectomy in conjunction with hepatectomy was performed in six patients. The hepatic resection bed was drained by two large closed suction drains.

The Intensive Care Unit (ICU) monitoring was used as necessary. Both colloid and crystalloid were used for volume replacement to compensate for expected postoperative fluid losses and excessive peritoneal drainage. Maintenance of fluid and hemodynamic balance was aided by flow-directed pulmonary artery catheterization and hemodynamic monitoring as necessary. Abdominal drains were removed when drainage volume was not excessive unless previous infection indicated prolonged drainage. Large volume abdominal drainage (3L>) was replaced volume:volume with lactated Ringers and albumin in the immediate postoperative period. Follow-up baseline data included abdominal CT scans and liver function tests at dismissal and three months after operation. In addition four patients had subsequent CT scans from 12 to 36 months after resection. Follow-up at the Mayo Clinic was arranged as medically necessary. The rest of our follow-up was by telephone interview.

Results

Eight women and one man underwent major hepatic resection for highly symptomatic PLD. The clinical features of these patients are summarized in Table 1. Patient

TABLE 1. *Clinical Findings of Patients with Polycystic Liver Disease Undergoing a Combined Hepatic Resection–Fenestration Procedure*

Patient	Age/Gender	Number of Pregnancies	Oral Contraceptive Use (Years)	Symptoms	ECOG
1	44/F	5	6	Abdominal pain, daily analgesics/narcotics	1
2	35/F	3	6	Abdominal pain, massive distention, early satiety, heartburn, nausea	1
3	43/F	2	6	Abdominal and shoulder pain, early satiety, regurgitation, heartburn	1
4	44/F	5	4	Abdominal pain, massive distention, early satiety, regurgitation, supine dyspnea	1
5	53/F	4	11	Abdominal pain, recurrent fevers, massive distention, early satiety, ascites, uterine prolapse, hemorrhoids	2
6	52/M	—	—	Massive abdominal distention, pain, rib fractures, ascites, dyspnea	2
7	68/F	5	0	Fever, nausea, emesis, pain	2
8	35/F	0	4	Abdominal pain, massive distention, supine dyspnea, heartburn, fatigue, ascites	2
9	50/F	2	15	Abdominal pain, massive distention, early satiety, diarrhea, supine dyspnea, ascites, hypotension during dialysis	2

TABLE 2. *Laboratory Findings Before Surgery and at Last Follow-up in Patients with Polycystic Liver Disease Undergoing a Combined Hepatic Resection–Fenestration Procedure*

	Before Surgery						Last Follow-up					
Patient	Renal Clearance (mL/min/1.73 M^2)	Serum Creatinine (mg/d L)	Aspartate Aminotransferase (u/L)	Alkaline Phosphatase (u/L)	Serum Bilirubin (mg/dL)	Serum Albumin (g/dL)	Duration of Follow-up (months)	Serum Creatinine (mg/dL)	Aspartate Aminotransferase (u/L)	Alkaline Phosphatase (u/L)	Serum Bilirubin (mg/dL)	Serum Albumin (g/dL)
1	109	0.9	18	167	0.8	4.1	8	0.9	20	137	0.9	3.0
2	74	0.9	16	125	0.8	3.8	36	0.9	25	95	1.0	4.3
3	33	1.8	20	59	0.5	3.9	27	1.8	22	76	0.8	4.3
4	33	1.7	16	146	0.6	3.8	27	2.0	15	121	0.4	3.9
5	Dialysis	Dialysis	13	208	0.4	3.3	18	Dialysis	14	208	0.3	3.5
6	34*	1.6*	35	339	0.8	3.6	—	—	—	—	—	—
7	—	1.4	31	551	0.5	2.9	12	2.2	21	292	0.5	4.1
8	68	0.9	28	159	0.6	2.7	4	0.9	32	192	0.3	4.0
9	Dialysis	Dialysis	14	201	0.7	3.3	2	Dialysis	14	196	0.6	3.7
Normal Range	80–120	0.7–1.1	12–31	70–196	≤1.1	3.5–5.0						

* Cadaveric renal transplant.

age ranged from 35 to 68 years and averaged 47 years. All women had either multiple pregnancies or had taken oral contraceptives. Specific symptoms included pain, massive abdominal distention, early satiety, nausea, regurgitation, heartburn, supine dyspnea, diarrhea, uterine prolapse, and hemorrhoids. Two patients had clinical evidence of cyst infection but only one patient had positive cyst fluid cultures. Three patients had clinical evidence of ascites and one hypotension during dialysis. Clinical performance status was impaired in each patient and was assessed as ECOG performance score 1 in four patients and 2 in five. The duration of disabling symptoms averaged 56 months, ranging from 8 to 144 months. Liver function tests were essentially normal, except for mild elevation of serum AST and alkaline phosphatase in one and four patients, respectively, and hypoalbuminemia in four (Table 2). Renal function was normal or relatively spared (serum creatinine less than 1.8 mg/dL) in six patients. Two patients required chronic hemodialysis and one patient had reduced but stable renal function 2 years after right nephrectomy, hepatic cyst fenestration, and cadaveric renal transplantation. Two other patients had previous abdominal explorations; one patient had a splenectomy and, on a separate occasion, an exploration only for a ruptured hepatic cyst, and another patient had transabdominal fenestration of left renal cysts.

All patients underwent multisegmental hepatic resection. Two to six liver segments were excised in each patient (Table 3). An example of a massively enlarged polycystic liver with segmental sparing before and after resection–fenestration is shown in Figure 1. The weights of the pathologic specimens ranged from 911 to 7600 grams and averaged 2869 grams. Because fluid was aspirated during cyst fenestration in each patient, the weight of the resected liver underestimated the net loss of mass in each patient. Weight loss during hospitalization ranged from 1.8 to 17 kg, with a mean of 6 kg. Six patients had a cholecystectomy and one had ligation of a splenic artery aneurysm and fenestration of multiple right renal cysts.

The average length of hospitalization was 15 days, with a range of 7 to 34 days and a median of 13 days. Six patients required intensive care, specifically for overnight observation of hemodynamics alone in 4 patients, 6 nights in 1, and 32 nights in the remaining patient.

The average duration of drainage was 13 days, with a range of 6 to 32 days. In eight patients abdominal fluid drainage varied from 10 to 5725 cc daily. Drainage exceeded 3000 cc per day for 8 consecutive days in one patient. Drainage was prolonged intentially in patients with preoperative cyst infection despite low volume output. Furthermore two patients on hemodialysis had prolonged, high-output drainage. Both of these patients had ascites after operation that gradually decreased in clinical significance. Volume and protein losses from peritoneal

TABLE 3. *Extent of Resection, Transfusion Requirements, Morbidity and Mortality, and Relief of Symptoms Undergoing a Combined Resection–Fenestration Procedure in Patients with Polycystic Liver Disease*

Patient	Hepatic Segments Resected	Blood/RBCs (units)	Duration (days)		Complications	Pain Relief	Abdominal Girth
			Drains	Hospitalization			
1	VII, VIII	2	6	7	None	↓	↓
2	VII, VIII	2	8	9	Right pleural effusion	↓↓↓	↓↓↓
3	VII, VIII	8	10	11	Right pleural effusion	↓↓↓	↓↓↓
4	II–VI, VIII	4	9	12	None	↓↓↓	↓↓↓
5	II, VII, VIII	8	14	16	Thrombosis of AV fistula	↓↓	↓↓
6	II, VI–VIII	61	32	34	Hypotension, coagulopathy, cholestasis, cerebral hemorrhage, death	—	—
7	V, VI–VIII	8	11	13	None	↓↓↓	↓↓↓
8	IV–VIII	6	13	14	Right pleural effusion	↓↓↓	↓↓↓
9	I–IV, VII, VIII	6	17	21	Thrombosis of AV fistula	↓↓↓	↓↓↓

Reduction of pain or girth: marked ↓↓↓, moderate ↓↓, minimal ↓.

drainage required careful monitoring and prompted infusion of a lactate Ringers solution and albumin to maintain fluid and protein balance.

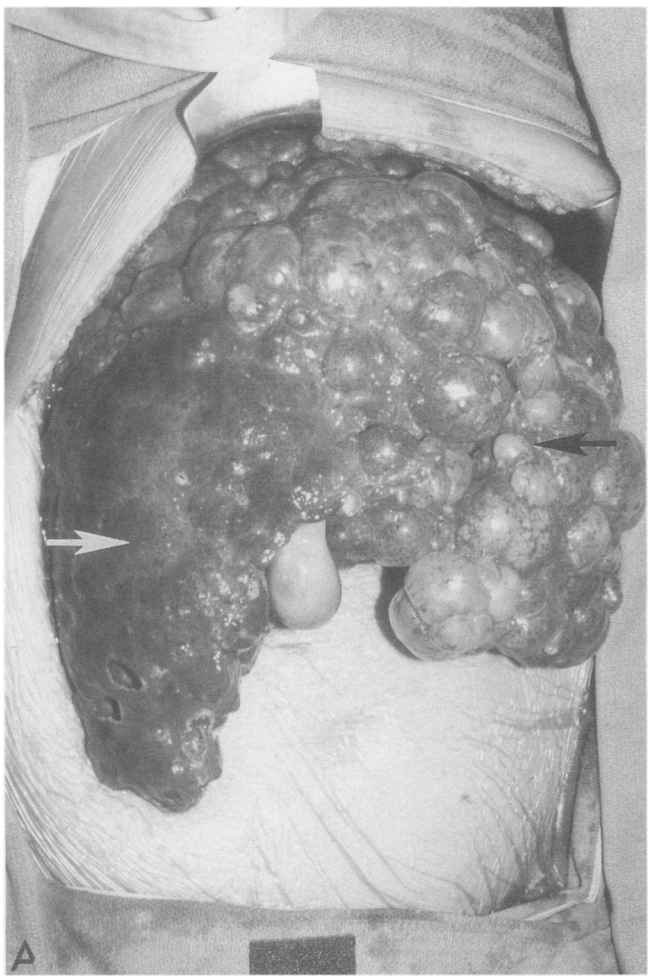


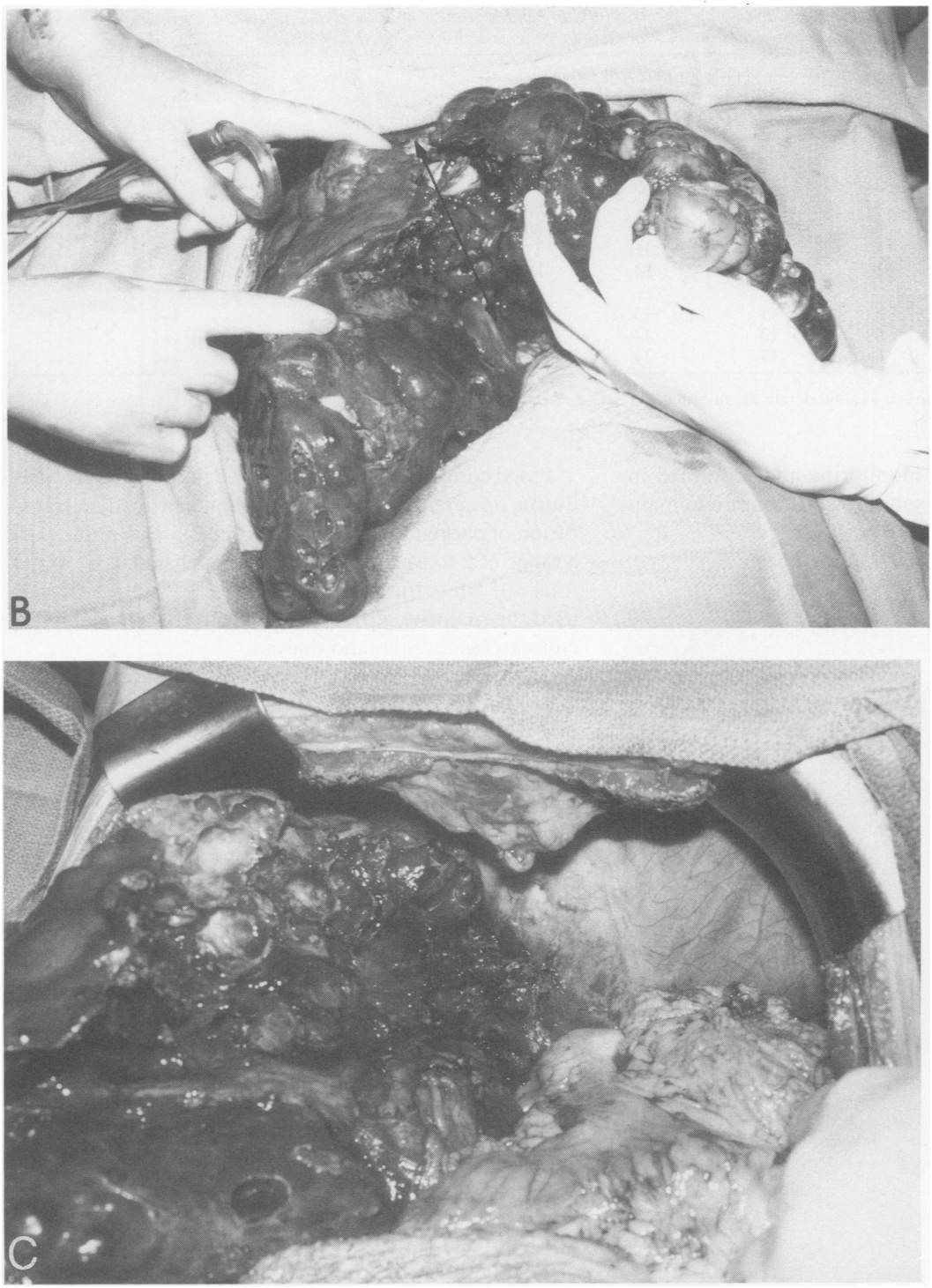
FIG. 1A. Intraoperative photographs of massively enlarged polycystic liver, showing polycystic liver (black arrow) and spared parenchyma (white arrow).

Blood components were transfused intraoperatively and during hospitalization in each patient. The median transfusion of packed red blood cells (PRBC) was 6 units, with a range of 2 to 61 units. One patient consumed 61 of the total 105 units transfused in our series. Another patient used the majority of her eight units in the course of vascular access revision and dialysis.

Three patients had a completely uncomplicated course. Three patients had transient right pleural effusions. Only one patient required thoracentesis. Two patients on dialysis had perioperative thrombosis of their arteriovenous fistula and required reconstruction of a new vascular access for dialysis.

Patient six had undergone previous hepatic cyst fenestration and renal transplantation and was receiving chronic immunosuppression. He had the most extensive liver involvement without sparing of two adjacent liver segments and required preoperative correction of malnutrition. His resection was complicated by intraoperative hemodynamic instability and consumptive coagulopathy. Transient hyperbilirubinemia and two episodes of sepsis complicated his postoperative course before his death due to an intracerebral hemorrhage. Although the death was presumed secondary to a ruptured berry aneurysm, an aneurysm was not confirmed at autopsy.

All surviving patients have experienced relief of abdominal symptoms and have returned to a normal performance status that has persisted for an average period of 17 months, with a range of 2 to 44 months of follow-up. Abdominal girth was reduced markedly in five patients, moderately in two, and minimally in one. The degree of abdominal girth reduction was related to the extent of resection, which increased as our experience grew. Reduction in liver size and abdominal girth was confirmed radiographically in all patients. Repeated abdominal CT scans in these patients have failed to show significant development of cysts in the previously spared liver segments during a mean follow-up period of 24 months. Indeed, as



FIGS. 1B and C. (B) Anticipated transection plane between spared and polycystic liver (double black arrow). (C) Remnant liver after left hepatectomy. Resection of cystic segments 7 and 8 was subsequently completed.

shown in Figure 2, CT scans have confirmed postresection hypertrophy of the spared liver and lack of clinically significant cyst progression. Liver function tests have remained stable (Table 2). Patient acceptance of the procedure has been considered good by seven patients responding favorably to questions of procedure worth and continued willingness to recommend the procedure based on their experience.

Discussion

Polycystic liver disease frequently develops in patients with ADPKD. Estimates of the prevalence of hepatic cysts

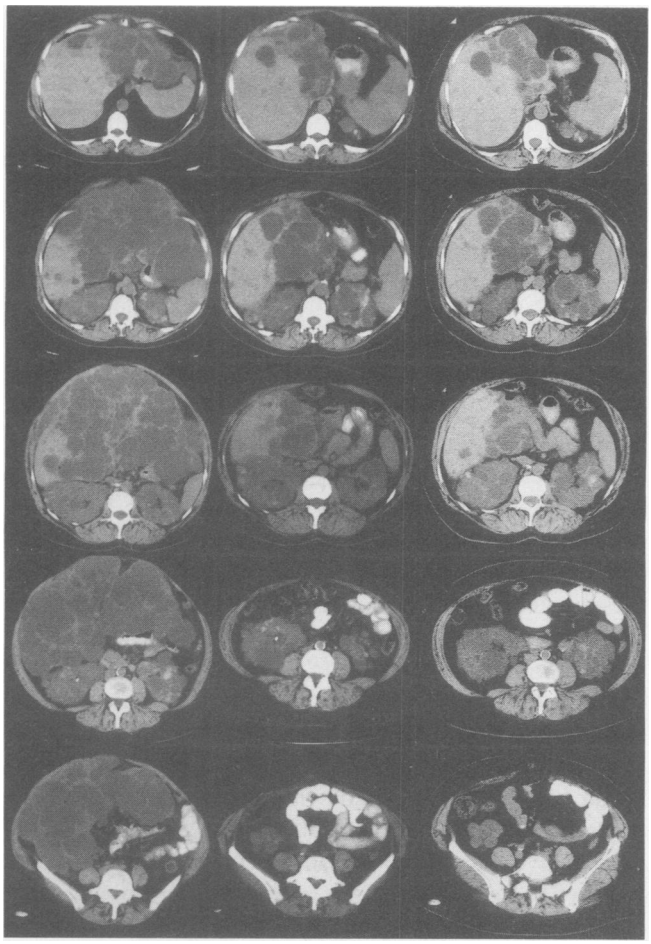


FIG. 2. Computed tomography of the abdomen in a patient with PLD before (left panels) and 3 months (central panels) and 3 years after (right panels) the combined resection–fenestration.

at autopsy have varied from 48% to 55% in patients with ADPKD.[1,2] Recent studies using ultrasonography and CT for liver imaging have confirmed an increased prevalence, which approached 100% in studies of long-term survivors after renal transplantation.[10,11] Risk factors associated with the development of polycystic liver disease in patients with ADPKD include increasing age, female gender, gravidity, and degree of impairment of renal function.[1–3,5,12,13] Despite this prevalence, hepatic cysts rarely cause symptoms or affect liver function. Indeed before renal transplantation, complications from renal cysts were the primary source of symptoms and death in patients with ADPKD.[1,2] As the treatment for chronic renal failure improved, survival of patients with ADPKD increased and, consequently, profound hepatocystic disease has become increasingly significant. Symptoms or complications from hepatic cysts are more frequent and a recent study of 229 patients with ADPKD has shown that 10.5% of deaths were from complications arising in hepatic cysts.[14]

Symptoms arise in patients with PLD from liver enlargement and compression of adjacent structures. Most symptomatic patients complain of increasing abdominal girth and a chronic dull abdominal pain. Liver enlargement may cause early satiety, weight loss, respiratory compromise, and physical disability.[13,15–21] Clinical performance status deteriorates and gross change in body habitus may become both physically and psychologically incapacitating. Acute severe pain may accompany cyst rupture or intracystic hemorrhage. Infection of hepatic cysts, especially in patients on chronic dialysis or in patients immunosuppressed after renal transplantation, may produce either subclinical or overt sepsis.[22–25] Portal hypertension,[26–28] obstructive jaundice,[29–33] and malignant degeneration[34,35] are rare complications. Hepatic failure in the polycystic patient has been reported very rarely.[27,36]

Nonsurgical treatment options for the few patients with incapacitating symptoms have been limited. Preliminary observations that hepatic cyst epthelia are sensitive to hormones that have an effect on the biliary system (*e.g.*, secretin) suggest that the natural history of these cysts might be influenced pharmacologically.[37] Whether reduction in extant cysts could be expected from hormonal therapy is unknown. Paliard et al.[38] found that cimetidine reduced the secretion rate of unroofed cysts, possibly by inhibiting gastric acidity and thus secretin-induced secretion. For patients who have only a few dominant cysts, percutaneous drainage has provided temporary relief.[39] Subsequent sclerosis using 95% ethanol or pantopaque has reputedly prolonged the relief afforded by percutaneous drainage.[40–42]

Simple cyst fenestration and peritoneal marsupialization have been the mainstays of surgical therapy. Fenestration had produced incomplete or temporary pain relief but rarely documented reduction in abdominal girth. Lin et al.[8] reported a more extensive fenestration procedure in three patients with PLD in whom successively deeper cysts were unroofed and drained through more superficial ones, resulting in significantly decreased hepatic symptoms. van Erpecum et al.[43] reported nine patients who underwent the Lin fenestration procedure. Although one patient died from hemorrhagic shock, abdominal complaints resolved in seven of the eight surviving patients. Furthermore obstructive jaundice and esophageal varices resolved in three of these patients. Howard et al.[29] also have reported resolution of biliary obstruction in one patient after Lin decompression. In practice, however, the efficacy of the Lin decompression for PLD is limited by extent of cysts, access to central cysts, postoperative walling off of cysts, and the rigid architecture of the fenestrated liver, which does not completely collapse.

For isolated cyst complexes, resection of the involved liver has been advocated.[44–46] Iwatsuki and Starzl[47] described two patients with extensive PLD who underwent right trisegmentectomy and right hepatectomy, respectively. Both patients had symptomatic relief.

In 1984 Armitage and Blumgart[9] reported one patient in whom sequential fenestration and resection were combined. Symptoms resolved and abdominal girth was reduced significantly. Their patient remained well during the 1-year follow-up period. The key modification by Armitage and Blumgart was that successive fenestration along a projected plane between diffusely cystic and spared parenchyma allowed safe resection of nonfunctioning symptomatic cystic mass with preservation of liver function. Thus the extent of fenestration was reduced and diffusely cystic volume was excised. Turnage et al.[48] reported three patients who also underwent combined resection–fenestration. Two of three patients had left lateral segmentectomies and one had a left lobectomy. Two of these patients died and consequently they reserve combined resection–fenestration for highly selected patients incapacitated by PLD. If the distribution of liver cysts in other patients with ADPKD would allow application of this combined technique, a realistic surgical option for highly symptomatic patients could be developed. Recently we reviewed abdominal CT scans from 119 patients with ADPKD and found massive liver involvement in 6 men and 18 women.[15] Twenty-one of these patients had relative sparing of two or more adjacent liver segments, thus confirming that resection is anatomically feasible in most patients.

Our experience with combined hepatic resection and fenestration shows that some patients with massive polycystic liver disease benefit markedly from this procedure. As our experience grew, we have performed extended hepatectomies in four patients. Our mortality and morbidity rates have been limited. Previously five patients have reportedly undergone major hepatic resection, *i.e.*, resection of more than three liver segments.[9,47–49] Careful identification of patients who have hepatic anatomy amenable to resection is imperative for the combined resection–fenestration. We used extensive preoperative evaluation to identify potential risks contraindicating resection by excluding patients with hepatic insufficiency, suspected malignancy, or significant cardiopulmonary compromise. Patients with malnutrition underwent preoperative correction to optimize nutritional status.

Two conditions may increase the operative risk of combined resection–fenestration for PLD. Previous abdominal surgery with abdominal adhesions between the liver and other viscera posed technical difficulties. In particular previous cyst fenestration resulted in more intense intra-abdominal adhesions. Therefore we advise patients with a history of previous surgery of the additional risks of bleeding or enterotomies. As a corollary we advocate cholecystectomy during hepatectomy to eliminate potential confounding diagnostic problems of postoperative biliary tract disease and to obviate the risk of subsequent cholecystectomy. Similarly we question whether a fully immunosuppressed patient should undergo major liver resection because of the complicated course of our only patient who had a functioning renal allograft. We could not determine which aspects of his medical history (extent of liver involvement, immunosuppression, previous liver surgery, cyclosporin A use, nutritional status) contributed primarily to his death. Interestingly coagulation abnormalities have been described in relation to cyclosporin A use, including microangiopathic hemolytic anemia and consumption coagulopathy.[50] None of the previously reported five patients who have undergone similar resections had comparable risk factors,[9,47,48] although one patient described by Turnage et al.[48] who had undergone previous liver surgery suffered a similar postoperative course.

Whether combined hepatic resection–fenestration should be used in patients with symptomatic PLD and concurrent renal failure is not clear. Although we have operated on two such patients, morbidity was greater in these patients than in our patients without renal failure. Combined single donor hepatic and renal transplantation offers an alternative solution to such patients. Clearly combined transplantation is indicated if both hepatic and renal failure are present. However hepatic failure is rare. We have been reluctant to advocate combined transplantation because liver-related symptoms can be effectively treated by resection–fenestration with preservation of normal liver function. Whether hepatic transplantation will ever be necessary in such patients is uncertain. Clearly current data supporting either treatment option is insufficient to recommend one preferentially. Follow-up studies examining the rate of cyst progression after resection and the early and late risk of allograft rejection from either sequential or combined multiorgan transplantation is needed.

The long-term benefit of combined hepatic resection and fenestration will be determined by postoperative progression of cystic degeneration in the spared liver remnant. Current data of the natural history of ADPKD and PLD suggest that progression of cystic disease will be slow, affording the possibility of prolonged benefit.[1–5] Although our follow-up is limited, clinical progression has not occurred in any of our patients. In contrast Iwatsuki and Starzl[47] observed cystic progression in two patients, 8 and 9 years after partial hepatectomy. We fully agree that hepatic transplantation should be used for disabling symptoms from progression of PLD after resection. Primary hepatic transplantation for PLD should be used preferably in patients without liver sparing or in rare patients with liver failure.

Acknowledgments

The authors thank Dr. D. W. Turner, Charlotte, North Carolina, and Dr. B. S. Daniels, University of Minnesota, who referred and assisted in the follow-up of two of the patients, and Dr. H. Zincke, who performed the surgical decompression of one kidney in one of the patients.

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