Treatment of Polycystic Liver Disease: One Size Does Not Fit All

Nearly all patients with autosomal dominant polycystic kidney disease (ADPKD) develop cysts in the liver as they age. In addition, polycystic liver disease (PLD) also exists as a genetically distinct disease in the absence of renal cysts. In both cases, liver cysts arise by excessive proliferation and dilatation of biliary ductules and peribiliary glands. Estrogen receptors are expressed in the epithelium lining the hepatic cysts and estrogens stimulate hepatic cyst-derived cell proliferation. This explains why hepatic cysts are more prevalent and hepatic cyst volume is larger in women than in men and why women who have had multiple pregnancies or used oral contraceptive agents or estrogen replacement therapy have worse disease than those who have not.

Typically, PLD is asymptomatic, but symptoms have become more frequent as the lifespan of ADPKD patients has lengthened with dialysis and transplantation. Symptoms may result from the mass effect of the cysts or from cyst complications such as rupture, hemorrhage, or infection. Symptoms related to mass effect can be caused by a single or limited number of large dominant cysts, by hepatic enlargement caused by numerous cysts of mostly small or medium size, or by strategically located cysts compressing intrahepatic structures such as the inferior vena cava, hepatic veins, portal veins, or bile ducts. These symptoms include dyspnea, early satiety, gastroesophageal reflux, mechanical low back pain, and less frequently those related to hepatic venous outflow obstruction (ascites), inferior vena cava compression (lower extremity edema, hypotension on dialysis), portal vein compression (portal hypertension), or bile duct compression (obstructive jaundice).

Most cases of PLD require no treatment. Rarely, symptomatic PLD requires interventions to reduce cyst volume and hepatic size. These interventions include percutaneous cyst aspiration without or with sclerosis, laparoscopic cyst fenestration, combined liver resection and cyst fenestration, and liver transplantation. In this issue of *AJKD*, Takei et al describe a new technique, selective hepatic artery embolization, to reduce polycystic liver size. These interventions are not interchangeable. Each one has specific indications that are dictated by the anatomy and distribution of the cysts and particular patient characteristics. In some cases, mass effect-related symptoms can be relieved by interventions not aimed at reducing cyst volume, such as inferior vena cava, hepatic vein, or bile duct stenting.

Percutaneous cyst aspiration under ultrasound or computed tomography (CT) guidance is helpful to establish causality between a particular cyst and symptoms, but it has no lasting result because the cyst fluid reaccumulates within weeks. Injection of an appropriate volume (25%...
of the aspirated cyst fluid) of 95% to 99% ethanol or acidic solutions of tetracycline or minocycline with positioning of the patient to ensure that all the cyst-lining epithelium has direct contact with these solutions can be used to ablate the cyst. Before instillation of the sclerosing agent, contrast media is injected into the cyst to rule out communication with the bile ducts (which could cause irreversible sclerosing cholangitis) or leakage into the peritoneum. This procedure is best suited for deep-seated cysts within the liver because the tissue pressure of the surrounding parenchyma helps to collapse the cyst (Fig 1). Properly performed, the procedure has minor complications. The success rate (approximately 70%) decreases for very large cysts (>10 cm in diameter) and some authors recommend repeating the injections on several consecutive days.

Laparoscopic fenestration of hepatic cysts in the setting of PLD should be reserved for cases where symptoms are caused by one or few large dominant cysts located superficially in anterior segments of the right lobe (segments IV through VI in Couinaud’s classification) or in left lateral segments (Fig 1). In properly selected patients, this procedure is successful in over 80% of cases. Wide excision of the cyst wall and concomitant argon beam coagulation or electrocoagulation of the unroofed cyst-lining epithelium have been recommended to reduce the risk of recurrence. Complications, mainly prolonged post-procedure drainage, transient ascitis, and bile leaks, may occur in up to 20% of patients.

Percutaneous sclerosis and laparoscopic fenestration are futile in highly symptomatic patients with massively enlarged polycystic livers with

Figure 1. (A) Deep-seated large cyst in the right hepatic lobe, approachable (at a lower level to avoid the lung) for cyst aspiration and alcohol sclerosis. (B) Superficial large cyst arising from the right lobe of the liver suited for laparoscopic fenestration. (C) Polycystic liver disease (PLD) involving both lobes, more severely segments VII and VIII; this patient is not a good candidate for combined liver resection and cyst fenestration because of the distribution of the cysts and involvement of the less severely affected segments by many small cysts with further potential for growth. This patient might benefit from embolization of hepatic artery branches supplying segments VII and VIII that have no recognizable hepatic parenchyma. (D and E) PLD before (D) and after (E) combined right lobectomy and cyst fenestration; note compensatory hypertrophy of the left lobe after surgery. (F) Massive PLD without relative preservation of any liver segment; the only feasible treatment in this patient is liver transplantation.
many cysts of small and medium size. Despite marked hepatomegaly, the volume of the non-cystic parenchyma is usually normal or even larger than normal and hepatocellular function is intact. Because in many cases the cystic disease affects certain hepatic segments more than others, combined resection of the severely affected segments and fenestration of cysts in the relatively spared segments is often possible and achieves an average reduction in liver size of 62% (from 9,357 mL to 3,567 mL) with sustained improvement in quality of life (Fig 1). A careful evaluation of the hepatic veins by magnetic resonance (MR) angiography is critical in planning for this surgery, since preservation of hepatic venous drainage is essential for its success. Because of a high rate of complications (including prolonged post-surgical drainage, transient ascitis and pleural effusions, bile leaks, and thrombosis of vascular accesses for dialysis) and a perioperative mortality of 3.2%, this surgery should only be performed in specialized centers by surgeons experienced in this procedure.

Liver transplantation is indicated in highly symptomatic patients in whom combined hepatic resection is not technically feasible and in rare patients with reduced hepatic function due to unrelated or related pathologies (Fig 1). Combined liver-kidney transplantation should also be considered in highly symptomatic patients with reduced renal function in whom combined liver resection/cyst fenestration may be technically feasible but is likely to be difficult and to have a complicated postoperative course.

Currently, organ allocation in the United States is based on MELD (Model for End-Stage Liver Disease) score by the United Network for Organ Sharing. Since PLD patients have normal liver function, their MELD scores are low. Progressive starvation and malnutrition while waiting in the transplant list and technical difficulties related to the massive size of the liver and in some cases adhesions related to previous surgeries contribute to the morbidity and mortality from liver transplantation in PLD. In the most recent reports, 5-year patient survival after liver or combined liver-kidney transplantation is approximately 85% with excellent quality of life. Most of the mortality occurs in the first 3 months following transplantation. It has been proposed that patients with highly symptomatic PLD who are not candidates or fail to respond to non-transplant interventions and have severe malnutrition (serum albumin <2.2 g/dL [<22 g/L] or mid-arm circumference in the non-dominant arm <23.1 cm in female patients and <23.8 cm in male patients) should be listed for liver transplantation and receive an initial MELD score of 15 if the creatinine clearance is greater than 30 mL/min (>0.5 mL/s), or 20 if the creatinine clearance is less than 30 mL/min (<0.5 mL/s), and, in both cases, that the score should be increased by 3 points every 3 months.

In this issue of AJKD, Takei et al propose that selective hepatic artery embolization can be used to achieve mass reduction in patients who are not candidates for combined liver resection and cyst fenestration or for liver transplantation. They describe their experience in 30 patients (22 of them on dialysis) with follow-up CTs 18 to 37 months after embolization. The procedure appeared to be safe and well tolerated with pain and fever that resolved within 5 days as the main side effects. However, the average reduction in liver size (from 7,882 mL to 6,041 mL) was less than that achieved by combined liver resection and cyst fenestration (22% compared to 62%). This may be in part due to the fact that this technique only targets hepatic regions without intact hepatic parenchyma, while surgical resections target regions with severe cystic disease which may still contain areas of normal hepatic parenchyma between the cysts (Fig 1). Embolization of segments with occluded portal veins may carry a risk of hepatic necrosis, but this may not be a problem when there is so little normal liver parenchyma remaining. More experience with selective hepatic artery embolization by other groups is needed to confirm the safety and efficacy of this procedure. Currently, it may be best suited to treat highly symptomatic patients who have large areas of cystic liver without recognizable hepatic parenchyma and are not good candidates for combined liver resection and cyst fenestration.

Recent advances in the molecular genetics and biology of polycystic kidney and liver have shed light on its pathogenesis and raised the hope for therapies to delay, inhibit, or even reverse cyst development. Alterations in 2 major interacting second messengers, intracellular calcium and cyclic AMP (adenosine monophosphate), modu-
late cystogenesis by promoting fluid secretion and cell proliferation. Octreotide, a synthetic, metabolically stable somatostatin analog, has been shown to inhibit cAMP accumulation in the bile ducts and to halt the expansion of hepatic cysts from polycystic kidney (PCK) rats in vitro and in vivo. Octreotide, a synthetic, metabolically stable somatostatin analog, has been shown to inhibit cAMP accumulation in the bile ducts and to halt the expansion of hepatic cysts from polycystic kidney (PCK) rats in vitro and in vivo. Octreotide, a synthetic, metabolically stable somatostatin analog, has been shown to inhibit cAMP accumulation in the bile ducts and to halt the expansion of hepatic cysts from polycystic kidney (PCK) rats in vitro and in vivo. Octreotide, a synthetic, metabolically stable somatostatin analog, has been shown to inhibit cAMP accumulation in the bile ducts and to halt the expansion of hepatic cysts from polycystic kidney (PCK) rats in vitro and in vivo. Octreotide, a synthetic, metabolically stable somatostatin analog, has been shown to inhibit cAMP accumulation in the bile ducts and to halt the expansion of hepatic cysts from polycystic kidney (PCK) rats in vitro and in vivo.

A clinical trial of long-acting release octreotide for patients who are not candidates for or who decline surgery for severe PLD is currently in progress.

Vicente E. Torres, MD, PhD
Mayo Clinic College of Medicine
Rochester, Minnesota

REFERENCES
17. Kirchner GI, Rifai K, Cantz T: Outcome and quality of life in patients with polycystic liver disease after liver or combined liver-kidney transplantation. Liver Transpl 12:1268-1277, 2006