

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Polycystic Liver Disease



**Stuart C. Gordon, MD**  
 Director of Hepatology  
 Department of Gastroenterology and Hepatology  
 Henry Ford Health System  
 Professor of Medicine  
 Wayne State University School of Medicine  
 Detroit, Michigan

### G&H What is polycystic liver disease?

**SG** Polycystic liver disease (PLD) is a collection of disorders that is usually, but not always, seen in association with polycystic kidney disease. PLD coexists with both the autosomal dominant and recessive forms of polycystic kidney disease and represents the end result of cholangio-cyte-derived cysts within the liver that ultimately replace liver tissue.

### G&H How do the subtypes of PLD differ?

**SG** The more common form of PLD is an extrarenal manifestation of autosomal dominant polycystic kidney disease. The less common form of isolated PLD is an autosomal dominant inherited condition and has been associated with 2 distinct mutations: the *PRKCSH* gene that encodes for hepatocystin and the *SEC63* gene that encodes for a component of the protein translocation machinery in the endoplasmic reticulum.

### G&H What is the genetic basis of PLD?

**SG** The disorders that make up PLD are characterized by defects in the ductal plate during embryologic development. Such ductal plate abnormalities may occur at various levels. Thus, PLD has a wide clinical spectrum that ranges from von Meyenburg complexes (ectatic microscopic bile ducts, also known as microhamartomas) to giant hepatic

cysts. Recently, a newer definition for these ductal plate malformations was proposed, classifying 3 distinct mechanisms: abnormal hepatoblast differentiation, failure of bile duct maturation, and perturbation of ductal expansion.

### G&H What other risk factors are associated with this condition?

**SG** PLD is more common among women. Additionally, women with PLD generally have more severe manifestations. There has been a suggestion in the literature that multiple pregnancies or perhaps exposure to exogenous estrogens may hasten disease progression. The disease is not common among children, whereas advancing age is a recognized risk factor.

### G&H What clinical symptoms should raise suspicion of this condition?

**SG** Clinical manifestations are variable. Asymptomatic patients may have incidental cysts noted on routine imaging performed for other reasons. Nonspecific symptoms may include postprandial fullness or even back discomfort. Occasionally, the first presentation may occur after spontaneous cyst hemorrhage and acute abdominal pain, which usually abates without sequelae. These cysts may be solitary or spread diffusely throughout the liver. There appears to be a higher prevalence of multiple cysts among older individuals.

## G&H How does early PLD differ from advanced PLD?

**SG** The differentiation between early and advanced PLD is a clinical distinction, usually based upon symptoms. It should be emphasized that many patients with PLD remain entirely asymptomatic throughout their lives and only discover their disease upon routine liver imaging. Other patients may present with varying degrees of abdominal discomfort or fullness. Massively enlarging cysts likely create symptoms via cyst compression of the peritoneum and resultant peritoneal irritation as opposed to stretching of the Glisson capsule per se. A noxious and constant discomfort ensues, occasionally with sharp pain. The larger cysts, especially if located on the left lobe, may compress adjacent visceral structures such as the stomach, with advanced anorexia and gastroesophageal reflux symptoms. Patients rarely present with jaundice because of cyst compression of bile ducts, or ascites and other signs of portal hypertension owing to cyst compression of vascular structures, including the inferior vena cava.

As the cysts continue to enlarge, they create a clinical impression of massive hepatomegaly, with pain causing considerable abdominal discomfort, which may diminish the patient's quality of life. On occasion, these cysts may bleed spontaneously, causing acute abdominal pain; they may also, on rare occasion, rupture, but these incidents are usually not life-threatening.

## G&H Is treatment always warranted in patients with PLD?

**SG** Management is based upon symptomatic presentation. Because of the potential association of this condition with contraceptive corticosteroid preparations, such agents and estrogenic supplements should be discontinued. Over-the-counter analgesics, including acetaminophen at therapeutic doses, are acceptable for symptomatic relief. Often, no specific therapy is warranted, as therapy is directed toward symptoms and the patient may be asymptomatic.

## G&H How is PLD usually treated?

**SG** Early literature demonstrated that cyst aspiration for symptomatic relief is followed by rapid fluid reaccumulation. Treatment of symptomatic patients may include percutaneous aspiration and drainage by interventional radiologists, although such remedies are by definition transient and perhaps diagnostic to assess the degree to which the cysts are causing the symptoms. Laparoscopic cyst fenestration or unroofing is an option for more symptomatic patients, and such procedures should ideally be performed at centers with

expertise in this fairly uncommon surgical technique. Liver resection is technically more difficult, and liver transplantation may be an option in some cases.

## G&H When is invasive treatment recommended?

**SG** Surgical unroofing, which can be performed laparoscopically, should be considered when adjacent structures are being compressed. Thus, surgical options should be reserved for the most symptomatic patients who have become incapacitated by massive liver enlargement. Recent case reports have shown the benefit of inferior vena cava stent placement for the purpose of decompression when portal hypertension resulting from inferior vena cava obstruction is causing refractory ascites. Liver transplantation may be reserved for rare and highly symptomatic cases. However, thought should be given to transplantation when partial hepatectomy is being considered, as one study suggested that such surgery might render future transplantation more problematic.

## G&H How effective is liver transplantation as a therapeutic option in this setting?

**SG** A recent review of 28 patients who underwent orthotopic liver transplantation at a single center over a 20-year period showed very good overall results, but it also showed that previous disease-directed interventions tended to mitigate favorable transplant outcomes. The authors concluded that patients had excellent long-term graft and patient survival but that previous open disease-directed interventions were associated with increased risks of perioperative morbidity and mortality.

It should also be noted that, based on the recent guidelines from the Organ Procurement and Transplantation Network, it is becoming increasingly more complex to qualify for exception points for orthotopic liver transplantation for PLD in the United States. Many otherwise transplant-eligible candidates may not qualify for this most definitive of therapies.

## G&H What pharmacologic options are available?

**SG** Somatostatin analogues have been tested to help reduce cyst volume and provide symptomatic relief in cases of PLD. A recent pooled analysis of 2 randomized, double-blind, placebo-controlled trials examined 96 patients with PLD treated between 6 and 12 months, and patients completed standardized health-related quality-of-life questionnaires. This study concluded that somatostatin analogues improve health-related quality of life in symptomatic PLD and hepatomegaly.

Similarly, a recently published prospective study of 53 patients with PLD showed that low doses of lanreotide

(90 mg every 4 weeks) reduced liver volumes and symptoms in patients with PLD. However, patients continued to lose weight and muscle mass.

As noted in a recent review of PLD therapies, however, more effective treatments are needed because somatostatin therapy is not associated with significant benefits, long-term maintenance, or low cost. Potential therapies, including mechanistic target of rapamycin (mTOR), might in theory affect hepatic cyst growth and are being investigated in preclinical trials. Although a 2008 pilot trial of 16 patients with autosomal dominant polycystic kidney disease demonstrated that sirolimus, an mTOR inhibitor, reduced PLD volume by 26%, a more recent trial showed that adding everolimus to octreotide in PLD (vs octreotide alone) did not result in an additive effect in terms of liver volume.

Lastly, ursodeoxycholic acid was recently shown to halt the liver disease of a rat model of PLD by inhibiting cystic cholangiocyte hyperproliferation and decreasing the level of cytotoxic bile acid species in the liver. The authors proposed that ursodeoxycholic acid should be considered as a potential therapeutic tool for PLD patients.

*Dr Gordon has no relevant conflicts of interest to disclose.*

## Suggested Reading

Baber JT, Hiatt JR, Busuttill RW, Agopian VG. A 20-year experience with liver

transplantation for polycystic liver disease: does previous palliative surgical intervention affect outcomes? *J Am Coll Surg*. 2014;219(4):695-703.

Chrispijn M, Gevers TJ, Hol JC, Monshouwer R, Dekker HM, Drenth JP. Everolimus does not further reduce polycystic liver volume when added to long acting octreotide: results from a randomized controlled trial. *J Hepatol*. 2013;59(1):153-159.

Crossen WR, Drenth JP. Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. *Orphanet J Rare Dis*. 2014;9:69.

Gevers TJ, Inthout J, Caroli A, et al. Young women with polycystic liver disease respond best to somatostatin analogues: a pooled analysis of individual patient data. *Gastroenterology*. 2013;145(2):357-365.e1-2.

Munoz-Garrido P, Marin JJ, Perugorria MJ, et al. Ursodeoxycholic acid inhibits hepatic cystogenesis in experimental models of polycystic liver disease [published online June 1, 2015]. *J Hepatol*. doi:10.1016/j.jhep.2015.05.023.

Neijenhuis MK, Gevers TJ, Nevens F, et al. Somatostatin analogues improve health-related quality of life in polycystic liver disease: a pooled analysis of two randomised, placebo-controlled trials [published online July 1, 2015]. *Aliment Pharmacol Ther*. doi:10.1111/apt.13301.

Organ Procurement and Transplantation Network. Guidance on MELD PELD exception review. Guidelines for polycystic liver disease. <http://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/#PLD>. Updated June 2, 2015. Accessed July 16, 2015.

Qian Q, Du H, King BF, et al. Sirolimus reduces polycystic liver volume in ADPKD patients. *J Am Soc Nephrol*. 2008;19(3):631-638.

Raynaud P, Tate J, Callens C, et al. A classification of ductal plate malformations based on distinct pathogenic mechanisms of biliary dysmorphogenesis. *Hepatology*. 2011;53(6):1959-1966.

Temmerman F, Ho TA, Vanslebrouck R, et al. Lanreotide reduces liver volume, but might not improve muscle wasting or weight loss, in patients with symptomatic polycystic liver disease [published online June 11, 2015]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2015.05.039.

Tseng J, Orloff SL. Management of symptomatic polycystic liver disease with hepatic resection. *JAMA Surg*. 2015;150(1):81-82.