

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Polycystic Liver Disease

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### G&H Could you describe the manifestations of polycystic liver disease?

**GE** There are two forms of polycystic liver disease: polycystic liver disease in isolation, in which patients have cysts only in the liver, and autosomal dominant polycystic kidney disease, in which patients have cysts in both the liver and the kidney. The latter form is more common, representing 80–90% of all polycystic liver cases. Both forms of the disease are genetically determined. In patients with autosomal dominant polycystic kidney disease, the kidney component often dominates the clinical picture, as the patients can develop renal failure and require dialysis and/or kidney transplantation. In contrast, it is very rare for patients with polycystic liver disease to require hepatic transplantation, though it can occur if the symptoms or complications are unresponsive to or unmanageable with other interventions.

### G&H What is the current understanding of the pathophysiology of this disease?

**GE** Isolated polycystic liver disease has been associated with the genes *SEC63* and *PRKCSH*. The protein products of *SEC63* and *PRKCSH* (*sec-63* and hepatocystin, respectively), are involved in protein processing, and mutations in these genes affect proteins such as polycystin-1 and polycystin-2, which are associated with the transport of fluid and the growth of epithelial cells. Fluid secretion and epithelial proliferation are the two dominant mechanisms for the formation and growth of cysts.

As for autosomal-dominant polycystic kidney disease, at least two other genes, *PKD1* and *PKD2*, have been identified. *PKD1* and *PKD2* transcribe messages that translate into two key proteins, polycystin-1 and

polycystin-2, which normally regulate fluid secretion and growth of biliary epithelial cells. Mutations in *PKD1* and *PKD2* change the function of polycystin-1 and polycystin-2, favoring dysregulated fluid secretion and abnormal dysregulated growth of cyst lining epithelium. The primary cilium of biliary epithelial cells is a mechanosensor that regulates calcium influx into the biliary epithelial cell, which in turn regulates fluid secretion and growth of the epithelial cells. Polycystin-1 and polycystin-2 co-localize to the primary cilium, as do several other proteins that have been linked to cystic disease in either the kidney or liver. Mutations in these proteins alter the mechanosensory function of the primary cilium, preventing or altering Ca<sup>++</sup> influx into the epithelial cell.

### G&H What factors make some patients more susceptible to massive polycystic liver disease than others?

**GE** The main risk factor for polycystic liver disease is having a family member with the disease. Because the inheritance pattern is autosomal-dominant, if one family member is affected, up to 50% of the other family members may develop the disease. Normally, an index case in the family mandates screening of other family members; the general population is not screened because polycystic liver disease is relatively uncommon and the yield from screening would be low.

The most significant factor contributing to massive polycystic liver disease is female sex. Women are uniquely susceptible to massive polycystic liver disease, as opposed to men who have the same genetic mutation. It is believed that female steroid hormones may influence several of the factors responsible for secretion by and growth of liver cysts. In my studies, and in studies conducted by others, the risk of having massive polycystic liver disease is related to female gender, pregnancy, and exposure to exogenous sources of female steroid hormones such as contraceptive steroids or use of female hormone replacement therapy by postmenopausal women.

Another significant risk factor is age, as liver cysts appear to increase in size and number with age. In autosomal dominant polycystic kidney disease, both the severity of renal cystic disease as well as renal dysfunction appear

to promote more extensive hepatic cystic disease. Other metabolic factors or lifestyle factors, such as diet or smoking, have not been examined carefully in terms of whether they contribute to hepatic cystic disease.

### **G&H** What are the main symptoms of polycystic liver disease?

**GE** The main symptom of polycystic liver disease is abdominal distension due to the large mass of cysts in the liver. Other symptoms that are also caused by the large bulk of cysts within the abdomen include shortness of breath, early postprandial fullness, abdominal discomfort, and back discomfort. If a patient presents with these symptoms, they should undergo ultrasound or computed axial tomography imaging of the abdomen, which would immediately reveal the diagnosis. The characteristic findings on abdominal imaging are hepatomegaly and multiple macrocysts within the liver, in cases of isolated polycystic liver disease, or liver and kidney, in cases of autosomal dominant polycystic kidney disease.

It is rare for polycystic liver patients to present with specific liver problems such as jaundice, ascites, variceal bleeding, or encephalopathy. Occasionally, the liver cysts will impinge on the vascular structures of the liver, leading to portal hypertension and variceal bleeding. Patients with liver cysts can also experience impingement on the venous drainage of the liver, causing a “pseudo” Budd-Chiari syndrome, which blocks the venous drainage from the liver. Rare complications such as infection can arise in the cysts themselves, in which case patients may present with fever and pain local to the liver. Extremely rarely, patients can develop cystic carcinoma, which also typically presents with pain. However, by the time that cystic carcinoma is normally diagnosed, the patient often has fairly extensive disease and other symptoms such as weight loss.

### **G&H** Could you discuss the main treatment options for these patients?

**GE** It is often mistakenly believed that polycystic liver disease is a benign disease that does not require treatment or does not have treatment options available. However, symptom relief can be achieved with many of the interventions. Currently, the main treatment options for polycystic liver disease are primarily surgical or radiologic. The most widely used treatments involve reducing the bulk of the cystic liver. Usually, a stepwise approach is undertaken if the patient has several very large hepatic cysts evident upon imaging of the abdomen. The first option is usually abdominal percutaneous puncture, in which a radiologic technique is utilized to percutaneously insert catheters into the cysts in the liver. The fluid is subsequently drained and alcohol instilled into the cyst. This procedure can provide some temporary relief.

The next option for patients who either are not candidates for or who have failed the first approach would be laparoscopic cyst fenestration, in which the surgeon cuts windows into the cyst during laparoscopy, draining the fluid into the peritoneal space, where it is absorbed by the peritoneal lining. Occasionally, instead of performing cyst fenestration laparoscopically, the surgeon may opt to perform an open cyst fenestration procedure for improved exposure and a wider field.

Subsequently, the next step for treatment options involves either resection of the liver or liver transplantation. These are the procedures of last resort; they are reserved for patients with the most symptomatic disease or those who have failed the other approaches. Resection has several associated complications, including significant morbidity and even mortality. Resection and transplantation are technically difficult in these patients due to the massive size of the liver and distortion of usual anatomic landmarks. Generally, our surgeons at the University of Colorado have favored transplantation over hepatic resection in the surgical treatment of patients with polycystic liver. If a patient has to choose between either resection or transplantation, our surgeons have typically recommended transplantation, though in some centers resection has been utilized with at least partial success.

### **G&H** How safe and effective is liver transplantation in patients with polycystic liver disease?

**GE** Liver transplantation is not a simple procedure in polycystic patients, as the size of the liver and the impingement of the adjacent structures in these patients makes transplantation difficult. The early mortality rate from performing the operation ranges from 10% to 20%, though once patients recover from the immediate postoperative period (approximately 3 months), their long-term survival after transplantation is excellent. Many patients with polycystic disease who choose to undergo transplantation are quite pleased, as it resolves most if not all of their symptoms. Nevertheless, transplantation should not be undertaken lightly; as mentioned above, it does carry a significant risk of morbidity and mortality, of which patients must be made aware.

### **G&H** Does medical therapy play a role in the treatment of these patients?

**GE** Medical therapies for polycystic disease are currently under intensive investigation in clinical trials. Approximately 10–15 years ago, studies suggested that cysts in humans respond to hormones, particularly the secretory hormone secretin. Octreotide, which blocks the effects of secretin, was subsequently tried in anecdotal cases of polycystic liver disease. Unfortunately, in these small reports,

no definite benefit was evident with octreotide or with somatostatin, which was also tested. Similarly, there have been anecdotal reports regarding the use of estrogen receptor antagonists, but no obvious benefit has been observed. The main frustration of treating polycystic liver disease lies with the lack of effective medical and maintenance therapies, though there is optimism that ongoing trials may offer new weapons in the battle against the disease.

### G&H Could you discuss the medical therapy currently under investigation for polycystic liver disease?

**GE** Recent studies, mainly in animal models and cell culture systems, have revealed tantalizing bits of evidence that modification or regulation of key metabolic pathways by drugs or other agents can normalize secretion and growth of cystic epithelium. The strategies under study may lead to effective medical intervention for polycystic liver disease and autosomal-dominant polycystic kidney disease. Reports from current clinical experience also suggest that certain medical therapies may be effective in our patients. There are three main targets of this research.

The first target is the vasopressin-2 receptor. Vasopressin-2-receptor antagonists inhibit adenylate cyclase and reduce intracellular levels of cyclic AMP, which, in turn, diminishes secretion. Studies of an animal model of polycystic kidney disease have demonstrated that the vasopressin-2-receptor antagonist tolvaptan can reduce cyclic AMP and secretion. These findings and others have stimulated interest in the use of these agents in humans with autosomal dominant polycystic kidney disease; a therapeutic trial is now enrolling patients in both the United States and Europe. However, this strategy is not likely to be effective in polycystic liver, as the biliary epithelial cells, from which hepatic cystic epithelium is derived, lack the vasopressin-2 receptor.

The second target is the somatostatin receptor. Another class of drugs currently under investigation include somatostatin receptor antagonists such as octreotide, even though they did not demonstrate much efficacy in earlier anecdotal isolated cases in humans. Recent studies in animal models, particularly animals with cystic liver disease, have demonstrated that octreotide may slow down the progression of liver cysts. Accordingly, investigators are currently conducting a multicenter trial of octreotide therapy in patients with polycystic liver disease.

The third target is the mammalian target of rapamycin (mTOR). mTOR is inappropriately activated in cystic epithelium, and this activation is thought to be responsible, at least in part, for the dysregulated proliferation of cystic epithelium. The mTOR inhibitor sirolimus has been demonstrated to block the disordered, unregulated proliferative response of polycystic epithelial cells. In addition, activation of mTOR in polycystic epithelial

cells, especially hepatic cystic epithelium, increases synthesis and secretion of vascular endothelial growth factor (VEGF). VEGF stimulates angiogenesis but also may act through an autocrine or paracrine mechanism to further stimulate growth of cystic epithelium. Blockade of mTOR by sirolimus also lowers VEGF levels. In addition, specific blockade of VEGF by a VEGF-receptor antagonist has been shown to halt progression and development of hepatic cysts in a mouse model of polycystic liver and kidney disease.

### G&H Have there been trials of sirolimus in the treatment of this disease?

**GE** A trial of sirolimus in patients with polycystic kidney disease who have undergone renal transplantation is currently ongoing. Investigators plan to investigate the effects of sirolimus on native polycystic kidneys and liver. Two publications, each of a small number of patients, have reported initial intriguing observations that suggest potential benefit of sirolimus in polycystic disease. Shillingford and associates examined polycystic patients after renal transplantation and found that use of sirolimus was associated with significant reduction in the volume of the native polycystic kidneys. Another study of a similar population of patients from the Mayo Clinic reported that use of sirolimus was also associated with significant reduction in the volume of hepatic cystic disease. These intriguing and promising findings need to be confirmed in larger randomized controlled trials. Also, one must caution against use of sirolimus for the general treatment of polycystic liver disease, as sirolimus is a potent immunosuppressant with significant potential side effects. Appropriately conducted clinical trials of efficacy, safety, dose, duration, and expense are needed.

### Suggested Reading

- Qian Q, Du H, King BF, Kumar S, Dean PG, et al. Sirolimus reduces polycystic liver volume in ADPKD patients. *J Am Soc Nephrol*. 2008 Jan 16 [Epub ahead of print].
- Masyuk TV, Masyuk AI, Torres VE, Harris PC, Larusso NF. Octreotide inhibits hepatic cystogenesis in a rodent model of polycystic liver disease by reducing cholangiocyte adenosine 3',5'-cyclic monophosphate. *Gastroenterology*. 2007; 132:1104-1116.
- Everson GT, Taylor MR. Management of polycystic liver disease. *Curr Gastroenterol Rep*. 2005;7:19-25.
- Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. *Proc Natl Acad Sci U S A*. 2006;103:5466-5471.
- Arrazola L, Moonka D, Gish RG, Everson GT. Model for end-stage liver disease (MELD) exception for polycystic liver disease. *Liver Transpl*. 2006;12:S110-S111.
- Robinson TN, Stiegmann GV, Everson GT. Laparoscopic palliation of polycystic liver disease. *Surg Endosc*. 2005;19:130-132.
- Everson GT, Taylor MR, Doctor RB. Polycystic disease of the liver. *Hepatology*. 2004;40:774-782.
- Sherstha R, McKinley C, Russ P, Scherzinger A, Bronner T, et al. Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. *Hepatology*. 1997;26:1282-1286.