ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Update on Polycystic Liver Disease

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G&H What is the current definition of polycystic liver disease, and what is the genetic basis for this disease?

SG We still do not have a clear definition of this disease, although a recent consensus statement defined it as the presence of more than 10 fluid-filled cysts within the liver. Polycystic liver disease can occur alone or in association with polycystic kidneys. Patients who also have kidney cysts are usually treated by nephrologists due to the risk of end-stage renal disease and its complications. Isolated polycystic liver disease is associated with synthetic liver dysfunction only in rare situations. One study estimated that polycystic liver disease occurred in 1 in 158,000 individuals, but this number was likely underestimated because most patients are asymptomatic and, therefore, undiagnosed.

The genetic basis for autosomal dominant polycystic liver disease is complex and demonstrates considerable genotypic and phenotypic overlap. Autosomal dominant polycystic kidney disease has been associated with 8 genes and is caused by variants in the *PRKCSH*, *SEC63*, and *LRP5* genes. It was recently proposed that patients should be categorized via phenotype and genotype for enhanced clarity and accuracy.

G&H What is the current understanding of the natural course of polycystic liver disease and of the involvement of the liver?

SG The natural disease course can vary greatly. Some patients can have scattered uncomplicated cysts, while other patients with the same mutation can have disease severe enough to require transplantation. Disease penetrance has been reported to be 80%; therefore, nearly 20% of individuals carrying the same mutation may have minimal or no disease. Because most patients with polycystic liver disease who undergo liver transplantation are women, it has been suggested that disease progression may be related to sex (likely estrogen). Although further research is needed, women with polycystic liver disease should probably avoid taking oral estrogen or contraceptive corticosteroid preparations.

Recent literature has revealed new insights into the involvement of the liver in patients with polycystic liver disease. Interestingly, although the disease is often associated with polycystic kidney disease that can result in renal failure, the presence of multiple liver cysts is usually not thought to cause liver disease. Nevertheless, some patients with polycystic liver disease do develop ascites. This phenomenon may be explained by a recent retrospective study by Dr Louise Barbier and colleagues. Among 125 patients with polycystic liver disease who underwent either hepatic resection or transplantation, 92% had hepatic venous outflow obstruction lesions. In these patients, 2 or more hepatic veins were involved, with subsequent development of venous collaterals, frequently with an increased risk for hemorrhage at surgery. Accordingly, the alteration in the noncystic liver parenchyma of such patients represents a new paradigm in that doctors should not necessarily assume that all patients with polycystic liver disease have healthy liver tissue in their noncystic regions. Moreover, some of these patients had peliosis and nodular regenerative hyperplasia as well, and

over 50% of the patients had fibrosis, occasionally severe, in both the centrilobular and even the portal areas. The researchers suggested that the lack of preoperative ascites in some patients could be explained by the absence of inferior vena cava cyst compression, which occurs slowly. This study has important implications for the way that doctors should view patients with polycystic liver disease. The potential presence of hepatic venous outflow obstruction in these patients could further justify the use of laparoscopic cyst decompression to maintain appropriate hepatic outflow. However, further research is needed.

G&H When is intervention needed?

SG Most patients with polycystic liver disease do not have symptoms, so intervention is rarely needed. However, on occasion, symptoms may be caused by large dominant cysts because of accelerated growth, compression of nearby organs, or other reasons. In a recent study, Dr Philip de Reuver and colleagues examined patients with simple liver cysts who received a referral for surgery (most often due to pain in the upper abdomen). Forty-six patients underwent surgery, while 49 patients received conservative management. Patients in the first group had a greater likelihood of being older, presenting with shortness of breath, and having larger cysts. Most of these patients underwent laparoscopic stapled excision, which had a complication rate of 20% and a low rate of recurrence; in addition, positive patient-reported outcomes were reported. Thirty-seven percent of patients in the other group reported having new or the same symptoms on follow-up (median, 71 months). No difference in long-term quality of life was found among the 2 groups of patients. The researchers concluded that surgery was mainly effective in the presence of large symptomatic cysts or when a conservative treatment approach was not successful. The researchers noted that the standard of care is laparoscopic treatment, although variations in the terminology used in older studies have muddled interpretation.

G&H What is the most recent research on the medical treatment of polycystic liver disease?

SG Reports of medical therapy have been largely anecdotal, and the results of treatment trials have been essentially negative. For example, recent trials of everolimus and ursodeoxycholic acid did not demonstrate significant benefit at either decreasing the volume of cysts or improving symptoms. However, somatostatin analogues have recently shown some promise. A large prospective randomized trial of patients with autosomal dominant polycystic liver and kidney disease recently compared lanreotide (120 mg subcutaneously over 4 weeks; n=93) vs the standard of care (n=82). Patients who received lanreotide had decreased height-adjusted liver volume at 120 weeks as well as 4 months after the final injection. Thus, the researchers concluded that this therapy should be considered to slow the growth of liver volume in patients with polycystic liver disease. Interestingly, this treatment effect was mainly present in women, possibly supporting the idea that estrogen may have a role in the growth of liver cysts. However, an accompanying editorial stressed the main limitation of this study—symptomatic disease only occurs when patients with polycystic liver disease develop cysts with volumes over 4000 to 5000 mL, but this criterion was met by only a small proportion of patients in both the active and control arms. Moreover, the patients in the study all had autosomal dominant polycystic kidney disease, so research is needed in patients with polycystic liver disease without renal impairment.

G&H What research has been conducted recently on more invasive treatment of this disease?

SG Large cysts in the liver may occasionally cause severe symptoms, especially abdominal discomfort that limits quality of life. Although liver transplantation can be considered for the most advanced cases, aspiration sclerotherapy has been advocated as a minimally invasive procedure to decrease the volume of the cysts. The simultaneous injection of ethanol or other sclerosants into the cavity of the cyst attacks the epithelium of the inner lining.

In a recent double-blind, placebo-controlled trial, 34 patients with large hepatic cysts were randomized to either intramuscular injections of the somatostatin analogue pasireotide (60 mg, long-acting release) or placebo (sodium chloride 0.9%). The patients were mostly female (n=32), and the mean age was 53.6 years. At 6 weeks, the efficacy of aspiration sclerotherapy was not improved with pasireotide compared to control, and both groups had a similar decrease in long-term cyst diameter. Thus, there does not appear to be an added benefit to injecting this somatostatin analogue compared to using standard aspiration sclerotherapy in the setting of large symptomatic cysts in the liver.

In addition, it remains unclear whether the success of aspiration sclerotherapy should be measured by quantitative evaluation of symptom improvement or by decrease in cyst volume. Dr Myrte K. Neijenhuis and colleagues examined patients with large hepatic cysts who underwent cyst aspiration, and compared patient-reported outcomes according to the Likert scale (ranging from much worse to much better) after 6 months. The researchers found that improved patient-reported outcomes were associated with a positive health change, but a proportional decrease

in the volume of cysts was not. Thus, the researchers concluded that a decrease in the diameter of the cysts is not an accurate reflection of the success of aspiration sclerotherapy based on the point of view of patients.

G&H Based on current guidelines, how difficult is it to obtain a liver transplant for the treatment of polycystic liver disease?

SG Patients with severe symptoms such as massive hepatomegaly, recurrent ascites, and malnutrition with sarcopenia may benefit from liver transplantation. The listing process often requires petitioning for additional Model for End-Stage Liver Disease (MELD) points that vary from region to region; otherwise, such patients are unlikely to have MELD scores high enough to obtain a liver transplant. Patients with autosomal dominant polycystic liver and kidney disease may qualify for simultaneous liver-kidney transplantation, which has high overall survival rates. In a recent review of the United Network for Organ Sharing database, after excluding patients infected with hepatitis C virus (prior to the current era of direct-acting antiviral agents), patients who underwent combined liver-kidney transplantation for polycystic liver and kidney disease had survival similar to that of patients who were transplanted for other indications. In addition, significantly better outcomes were seen in patients with combined polycystic liver and kidney disease than in patients with polycystic liver disease who only received a liver transplant.

Dr Gordon has no relevant conflicts of interest to disclose.

Suggested Reading

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