Management of polycystic liver disease

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Polycystic liver disease (PCLD) is characterized by multiple cysts throughout the liver. Patients may develop chronic intractable symptoms that may be debilitating. Others may develop medical complications that necessitate intervention. There is a variety of nonsurgical and surgical treatment options for symptomatic or complicated PCLD, which range from cyst aspiration and fenestration to liver transplantation. Studies have described variable efficacy and morbidity. Currently, there are no guidelines for the management of PCLD patients and the optimal intervention is controversial. This article reviews the pathogenesis, classification and spectrum of treatment options for PCLD.

Key Words: *Fenestration; Polycystic liver disease; Resection; Transplantation*

Traitement de la polykystose hépatique

La polykystose hépatique (PH) se caractérise par la présence de nombreux kystes dans le foie. Certains patients peuvent présenter des symptômes réfractaires chroniques pouvant s'avérer débilitants. D'autres peuvent présenter des complications médicales nécessitant une intervention. Il existe divers traitements chirurgicaux et non chirurgicaux de la PH compliquée ou symptomatique, qui varient de l'aspiration des kystes et de la fenestration à la transplantation du foie. Des études en ont décrit l'efficacité et la morbidité. À l'heure actuelle, il n'existe aucune ligne directrice pour le traitement des patients atteints de la PH, et l'intervention optimale prête à controverse. Le présent article fait le point sur la pathogenèse, la classification et les différents traitements de la PH.

Polycystic liver disease (PCLD) is a rare condition that is frequently associated with polycystic kidney disease (PCKD) but may also occur independently. The prevalence of PCLD is approximately 0.15% in the general population, with the majority going undetected (1,2). However, multiple simple hepatic cysts are common in the general population at 2% to 10%, and may be confused with PCLD. Most cases of PCLD are associated with the autosomal dominant PCKD, which has an incidence of one in 800. In these patients, up to 55% will develop PCLD (3,4). Isolated PCLD occurs in less than 20% of cases and is a condition independent of PCKD (1,2,5). In both forms of PCLD, more severe cystic involvement has been associated with increasing age and more severe renal dysfunction (4,6,7). In addition, sex and hormonal factors play an important role, with more extensive lesions in females and patients with a history of multiple pregnancies. Interestingly, massive hepatic cyst disease occurs almost exclusively in females (4,6). With ongoing advancements in dialysis and the medical management of PCKD, patients surviving longer will be at increased risk of developing symptoms and complications from PCLD progression. Management of PCLD will become an important issue in these patients, whose morbidity was previously limited to cystic kidney disease.

PATHOGENESIS

The pathogenesis of PCLD is incompletely understood. PCLD cysts are believed to originate from biliary epithelium or the hepatic lymphatic system. Everson et al (8) found that PCLD cyst epithelium had the functional characteristics of biliary epithelium. They found that hepatic cystic fluid, similar to biliary epithelial fluid, contained secretory IgA and low glucose concentrations, and may be secreted in response to secretin. Histological studies have shown that hepatic cysts originate from either biliary microhamartomas separate from the biliary tract or from peribiliary glands, and dilate over time to become gross cysts. This finding has been seen in both isolated PCLD and PCLD associated with PCKD (1,2). Once cysts develop, enlargement of pre-existing cysts appears to contribute more to hepatic enlargement rather than the development of new cysts (9).

Although the pathogenesis of isolated PCLD is similar to that of PCLD associated with PCKD, they have different genetic origins. Autosomal dominant PCKD has been linked to PCKD gene 1 and 2 mutations (10). Recently, mutations in the protein kinase C substrate 80K-H gene encoding for hepatocystin have been described to be associated with autosomal dominant PCLD (11-13).

CLINICAL MANIFESTATIONS

PCLD typically has a slowly progressive and benign course. Most patients are asymptomatic and the condition is usually discovered incidentally or in association with PCKD presentation. Symptoms from PCLD may arise from the grossly enlarged liver compressing adjacent organs or from hepatic complications of PCLD, of which the latter is relatively uncommon. The most common symptoms requiring intervention are abdominal distension, abdominal pain and early satiety (9,14). Other symptoms include fatigue, nausea, vomiting,

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and supine shortness of breath (9). Because prolonged symptoms and discomfort can lead to significant anorexia, malnutrition and physical disability, active management should be undertaken before these long-term complications occur. Acute medical complications are experienced in fewer than 5% of patients and may necessitate acute intervention. These include cyst hemorrhage, rupture, infection, uterine prolapse, obstructive jaundice, portal hypertension, transudative and exudative ascites, and Budd-Chiari syndrome (9,14-19). Noncystic manifestations of isolated PCLD include mitral valve abnormalities in approximately 20% of cases. However, unlike PCKD, cerebral aneurysms do not appear to be associated with PCLD (6). Fortunately, despite overwhelming hepatic cyst involvement, hepatic synthetic function remains preserved in almost all cases (6).

Management of PCLD requires consideration of other possible causes of multiple liver cysts because treatment can be markedly different. Other multicystic diseases of the liver include echinococcal (hydatid) cysts, neoplastic liver cysts (cystadenoma and cystadenocarcinoma) and liver metastases with central necrosis (neuroendocrine, colon, pancreas, kidney and ovarian). The combination of clinical presentation, serology, liver ultrasound and computed tomography (CT) scan usually leads to a diagnosis. Occasionally, a liver biopsy is required for definitive diagnosis.

CLASSIFICATION

The extent of hepatic cystic disease in PCLD may not correlate with the presence of symptoms. Some patients may develop symptoms from a relatively few large dominant cysts compressing adjacent organs. Other patients may not experience symptoms until there is diffuse cystic disease resulting in extensive hepatomegaly. Management of PCLD requires tailoring specific interventions to hepatic cystic anatomy and symptoms. Currently, there is no universally accepted classification scheme for PCLD. Two schemes have been described based on CT imaging. Morino et al (20) classified PCLD into type 1 and type 2 based on cyst size, number and location. Type 1 PCLD has large cysts located mainly on the liver surface, while type 2 PCLD consists of diffuse small cysts all over the liver. Gigot et al (21) stratified individuals based on cyst size, number and amount of hepatic parenchyma remaining. Patients with PCLD type I have a limited number (fewer than 10) of large (greater than 10 cm) cysts. Type II includes those with diffuse, medium-sized cysts with large areas of remaining parenchyma. Type III patients were defined as those with diffuse cysts of small to medium size with few areas of normal liver parenchyma.

TREATMENT

Most patients with PCLD are asymptomatic and therefore do not require active treatment. The main indications for treatment are acute cystic complications or debilitating symptoms, which are usually secondary to the mass effect of several cysts or a few large dominant cysts, or the combination of both. Occasionally, large cysts can be aspirated beforehand to determine symptoms that may be associated with PCLD. There are several interventions available and the goal is reduction in hepatic cyst burden sufficient to relieve the mass effect while taking into account the incompletely defined long-term efficacies and widely variable morbidities of each procedure. All studies to date are retrospective and, therefore, a direct comparison of the available procedures is problematic.

Management of PCLD complications such as cyst hemorrhage, obstructive jaundice and ascites has been reported with nonsurgical techniques. For patients with progressive symptomatic PCLD, current management options include cyst aspiration with sclerosis, open or laparoscopic cyst fenestration, combined hepatic resection and fenestration, and liver transplantation.

Cyst aspiration with sclerosis has been described as effective for intracystic hemorrhage and biliary obstruction (15,16). PCLD patients can rarely also develop varices and ascites from portal hypertension due to cyst compression of hepatic and portal vasculature. Transjugular intrahepatic portosystemic shunt (TIPS) has been traditionally contraindicated in PCLD. Presumably, the distorted hepatic architecture and risk of cyst entry with intraperitoneal hemorrhage make the procedure unfavourable from a technical perspective. However, there have been published case reports of the beneficial role of TIPS in PCLD (22,23). Case reports have also described the temporary use of mesocaval shunts and beta-blockers for refractory ascites and gastrointestinal varices, respectively (18,19). However, definitive treatment for portal hypertension is liver transplantation (18,19). Overall, TIPS in PCLD is a high risk procedure that should be limited to nonsurgical patients with intractable ascites due to PCLD, and should be performed at experienced centres. Patients with refractory portal hypertension may benefit from a shunt insertion but should be considered for liver transplantation.

Percutaneous cyst aspiration with ethanol sclerosis has the advantage of being the least invasive intervention and, therefore, has a more favourable procedural risk. Cyst aspiration alone has not been effective because of frequent cyst recurrence (24). The combination of cyst aspiration and sclerosis was first described for renal cystic disease. In 1985, Trinkl et al (25) extended this procedure to hepatic cysts, and studies (26-28) have since shown effectiveness for treating symptomatic simple hepatic cysts. However, the data for cyst aspiration and alcohol sclerosis in PCLD are sparse. Tikkakoski et al (26) reported the largest series (14 PCLD patients) and found recurrence of symptoms in 50% after 48 months; symptomatic recurrence, however, was due to development of untreated cysts as opposed to re-expansion of treated cysts. Another small study has also shown stability in hepatic cysts specifically treated with the combined technique (27). There is variable efficacy among studies and this is due to small studies with differing protocols in the concentration of alcohol, duration of alcohol exposure, number of sclerosis treatments per cyst, and number of cysts sclerosed per session (25-28). One study has reported low complication rates and very minimal morbidity limited to pain and fever (25). In the long term, however, the procedure may be associated with biliary sclerosis.

Percutaneous cyst aspiration and sclerotherapy are limited to PCLD patients with small numbers of large dominant cysts which may be the symptomatic lesions. It is technically limited by the number and accessibility of cysts. In patients with massive hepatomegaly due to multiple, diffuse cystic disease, the technique will probably not provide long-term relief because of insufficient cyst collapse. Larger studies with longer follow-up are required to further define the technical details and efficacy in PCLD. However, in patients who prefer a nonsurgical approach first or who are not surgical candidates, this may be the only available option.

The surgical option of cyst unroofing is also known as cyst fenestration. Open and laparoscopic fenestration has been described in the literature (20,29-35). The fenestration procedure involves wide excision of the outermost cysts, followed by fenestration to deeper cysts, leaving free communication of open cysts with the peritoneal cavity. Resorption of cystic fluid subsequently takes place via the peritoneum. The danger with fenestration with or without hepatic resection is postoperative ascites and prerenal acute renal failure. The peritoneal cavity may not have the capacity to resorb large outputs of cyst drainage, especially in advanced PCLD disease or extensive fenestration. Caution should be taken in those with extensive cyst disease, renal dysfunction and small body habitus with large livers.

Laparoscopic fenestration was initially described in 1991 by Z'graggen et al (29). Since then, there have been several relatively small reports with variable results. The largest study reported by Kabbej et al (30) described a relatively high morbidity (54%) and recurrence of symptoms (77%) among 13 patients. However, in another study, Katkhouda et al (31) selected more anatomically favourable cystic lesions and reported greater success with lower morbidity (33%) and lower recurrence of symptoms (11%). Katkhouda et al limited the procedure to PCLD patients with dominant cysts in the anterior segments of the liver. Morino et al (20) stratified seven PCLD patients undergoing laparoscopic fenestration into type 1 (large cysts mainly on the liver surface) and type 2 (small cysts throughout the liver), and similarly showed that patients with large superficial cysts had no recurrence of symptoms while 75% of type 2 patients had persisting or recurring symptoms. Another study has also shown benefit of this procedure among those with anatomically appropriate cystic disease (32). Postoperative morbidity is usually limited to transient ascites, pleural effusions and, rarely, biliary leak.

As previously mentioned, the largest studies have shown transient morbidity of 33% to 54% and a symptom recurrence of 11% to 77%. Patients with symptomatic large superficial cysts appear to benefit most from laparoscopic fenestration. It may be preferred over cyst aspiration and sclerosis in PCLD with more numerous superficial cysts or cysts not accessible by the percutaneous technique.

Lin et al (33) first described cyst fenestration as an open technique in 1968. Koperna et al (34) described the largest PCLD series with 34 patients who underwent open cyst fenestration. They reported relatively good efficacy with only 21% reporting a recurrence of symptoms after 74 months of follow-up. Farges and Bismuth (35) reported the second largest study and similarly described a low recurrence of 23%. Postoperative morbidity, however, was quite high at 69%. Gigot et al (21) described results among patients with more severe PCLD (Gigot type II and III) and showed a low recurrence (11%) of symptoms after 73 months of follow-up. Although they found that most patients had a stable liver volume postoperatively, 40% of PCLD type III patients experienced a 30% to 40% increase in liver volume on CT as early as 52 months afterwards. The most common postoperative complications were transient ascites and biliary leak.

Overall, the largest studies on open fenestration have suggested good efficacy in relieving symptoms with low recurrence (11% to 23%) and minimal mortality, even among patients with diffuse (Gigot type II) PCLD. However, the ability to maintain reduced liver volumes in diffuse PCLD with minimal hepatic parenchyma (type III) may be problematic. Longer term studies that stratify patients anatomically are needed because symptom recurrence usually occurs later, after three to five years. Although postoperative morbidity is relatively high (56% to 69%) with this procedure, it may be an acceptable risk for patients with severe, debilitating symptoms.

Combined hepatic resection with open fenestration has been offered as another option in PCLD. Open cyst fenestration alone may have only a minimal effect on PCLD patients with massive hepatomegaly and predominant symptoms of abdominal distension. The technique is limited by the extent of cyst exposure, access to central cysts, and the rigid architecture of PCLD livers that fails to completely collapse after fenestration alone (9). The combination of hepatic resection and cyst fenestration described by Armitage et al (36) in 1984 has since been reported in several studies (9,21,37-39). This technique has been proposed to be more effective in reducing overall hepatic volume. Reduction of gastric compression may be accomplished by resection of hepatic segments two and three. Studies documenting hepatic volumes postoperatively have shown up to 40% greater reduction with the combined procedure than with open fenestration alone (9,21). Symptom resolution appears to be maintained long term. The largest study by Que et al (9) described 31 PCLD patients. After a mean follow-up of 28 months (0.2 to 7.9 years), they demonstrated a recurrence of symptoms in only 3%. Although the postoperative morbidity rate was 58%, they were all transient; there was no hepatic dysfunction and only one mortality from intracranial hemorrhage more than 30 days postoperatively. In addition, hepatic volume remained stable in nearly all patients. In those with cyst progression, hepatic enlargement was due to expansion of pre-existing cysts as opposed to development of new cysts. The second largest series by Soravia et al (37) described 10 patients undergoing the combined technique and showed a relatively higher recurrence rate of 33% after a longer mean follow-up of 68 months, with 20% experiencing postoperative morbidity. Other studies (38,39) have shown recurrence rates between 0% and 50% and morbidity rates between 38% and 100%. Most postoperative morbidity is due to transient ascites, transient pleural effusions and biliary leaks. Despite significant liver resection, there have not been any reports of liver dysfunction or postoperative failure.

Combined hepatic resection and cyst fenestration appears to be as effective as open fenestration with an appreciable early morbidity rate. The procedure appears to benefit PCLD patients with extensive, massive hepatomegaly and severe symptoms of abdominal distension, where greater reduction of overall hepatic volume is required. In addition, the ability of this technique to offer a greater reduction in hepatic volume while maintaining hepatic function may be beneficial in the relatively young population of symptomatic patients who are at risk for further residual cyst enlargement.

Liver transplantation has been offered as possible curative and definitive treatment for PCLD. Kwok and Lewin (2) first reported liver transplantation for PCLD in 1988. However, there is concern over the appropriateness of organ transplantation for this group of patients without hepatic failure when resources are extremely limited. In addition to the perioperative and long-term immunosuppression risks, the risks of renal toxicity in a PCLD population where the majority has PCKD also need to be considered. Reports of centres undertaking this procedure are limited in number and size. Lang et al (40)

described the largest series: 17 PCLD patients with a high perioperative mortality rate of 29%, which were all due to infections. Although 50% of the remaining patients experienced complications requiring surgical intervention, they were all symptom-free at a mean follow-up of 4.4 years. Pirenne et al (41) reported a much lower perioperative mortality rate (6.25%) among 16 patients. They have suggested intraoperative techniques to reduce surgical complications due to the distorted anatomy in PCLD. Although morbidity was similar at 40%, only three patients experienced infections and all were also symptom-free at follow-up. Pirenne et al (41) proposed that the low mortality rate from infections was due to operating on less physically exhausted and nutritionally deficient patients, and the use of lower doses of immunosuppression. Other smaller studies have found similar mortality, morbidity and symptom-free rates (42,43). The most frequent postoperative morbidities were bleeding, hepatic arterial thrombosis, biliary leak, biliary stricture and infection. The relatively high mortality and morbidity rates among PCLD transplant patients imply that patients should be carefully selected. Only patients who are severely symptomatic and debilitated from PCLD should be considered. However, the procedure should be recommended before severe malnutrition develops, to reduce postoperative infection risk. Furthermore, it should be anatomically limited to those with extensive, small, diffuse cysts with little hepatic parenchyma, which makes other, more conservative, surgical options less feasible and effective (41). Transplantation may also be the only option for those who are refractory to previous nonsurgical and surgical interventions.

Because severe PCKD is frequently associated with severe PCLD, the issue of combined liver and kidney transplantation must also be addressed. This symptomatic patient population is frequently young, and long-term prognosis beyond hepatic issues focuses on renal disease. There is concern that progressive renal insufficiency may be hastened with nephrotoxic immunosuppression and PCKD progression. Jeyarajah et al (43) found that all liver transplantation patients with significant renal insufficiency (not yet end stage renal disease [ESRD]) eventually progressed to ESRD requiring renal transplant. Pirenne et al (41) found that after early follow-up (40% less than 32 months) of 13 PCKD or PCLD patients who underwent liver transplantation, only one patient (8%) eventually developed ESRD requiring renal transplantation. However, this patient had the greatest level of renal insufficiency (mild to moderate) of those who underwent liver transplantation alone, while the remaining had relatively normal renal function. Demirci et al (44) described the largest report on combined liver and kidney transplantation in 17 PCLD patients, most of whom were already on hemodialysis. They demonstrated a relatively good long-term survival rate of 82.6% with a mean follow-up of 4.2 years. Only one patient returned to hemodialysis and all had preserved liver function. Patients with ESRD or moderate renal insufficiency appeared to benefit from combined transplantation. Early studies suggest that patients with PCKD and normal renal function may not require combined transplantation; however, further studies with longer term follow-up are needed.

Liver transplantation may benefit selected debilitated PCLD patients with severe, diffuse, small cystic disease and little residual parenchyma. A combined liver and kidney transplant should be undertaken in those with significant renal disease. The liver transplantation mortality rate is not insignificant and postoperative morbidity requiring surgical reintervention is considerably higher than that of other more conservative operative techniques. However, it does offer the potential for cure, excellent symptom relief and improvement in quality of life from PCLD.

CONCLUSIONS

The management of PCLD is focused on individuals who are symptomatic or who have acute hepatic complications. There are several treatment options available and the indications for specific interventions are incompletely defined. Management of PCLD requires assessment of the cystic anatomy accounting for symptoms. Stratification of PCLD based on cyst size, location and number, and residual hepatic parenchyma is useful. Although longer term studies are needed, reports to date have shown benefits for multiple nonsurgical and surgical strategies in managing PCLD.

Percutaneous cyst aspiration and sclerosis benefit those with few large anterior cysts. Laparoscopic fenestration may be useful in patients with several large superficial cysts which may not be amenable to percutaneous treatment. Open fenestration appears to be effective in patients with diffuse cysts with large areas of parenchyma remaining. In patients with massive hepatomegaly and large areas of residual hepatic tissue, combined fenestration and resection is useful. Patients with diffuse, small cysts and little hepatic parenchyma may consider liver transplantation. A combined liver and kidney transplant should be considered in those with greater than moderate renal insufficiency. The management of PCLD should be placed in the hands of experienced clinicians with a specialized multidisciplinary approach.

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