Clinical management of polycystic liver disease☆

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Clinical vignette

A 41-year old female underwent a computed tomography (CT) scan in 2010 because of symptoms suggestive of appendicitis. Incidentally, multiple liver lesions characterised as cysts were detected. The presence of small to medium sized liver cysts (diameter between <1 cm and 4 cm) in all liver segments (>100 cysts) and absence of kidney cysts in the context of normal renal function led to the clinical diagnosis of autosomal dominant polycystic liver disease (ADPLD). Five years later she was referred to the outpatient clinic with increased abdominal girth, pain in the right upper abdomen and right flank, and early satiety. She had difficulties bending over and could neither cut her toenails nor tie her shoe laces. In her early twenties she had used oral contraception for five years. She has been pregnant twice. Clinical examination showed an enlarged liver reaching into the right pelvic region and crossing the midline of the abdomen. Laboratory testing demonstrated increased gamma-glutamyl transferase (80 IU/L, normal <40 IU/L) and alkaline phosphatase (148 IU/L, normal <100 IU/L) levels. Bilirubin, albumin and coagulation times were within the normal range. A new CT scan in 2015 was compatible with an increased number and size of liver cysts. The diameter of cysts varied between <1 cm and 6 cm (anatomic distribution shown [Fig. 2B]). There were no signs of hepatic venous outflow obstruction, portal hypertension or compression on the biliary tract. Height-adjusted total liver volume (htTLV) increased from 2,667 ml/m in 2012 to 4,047 ml/m in 2015 (height 172 cm).

The case we present here is not uncommon, and prompts several relevant questions:

  I. What causes the development of liver cysts?
  II. Is genetic testing and genetic counselling recommended?
  III. What is the natural course of polycystic liver disease and what can patients do to stop growth of liver cysts?
  IV. Which complications may occur during the course of polycystic liver disease?
  V. What treatment options are currently available?
  VI. What other potential new and effective therapies will be available in the near future?

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Introduction

Polycystic liver disease (PLD) is characterised by the presence of multiple fluid-filled liver cysts. PLD can be diagnosed using ultrasonography, CT scan or magnetic resonance imaging (MRI). Although a clear definition of PLD is absent, current literature defines PLD as >20 liver cysts.[1] Recently the international PLD Registry steering committee, consisting of experts who have extensive experience and knowledge in the field of PLD, came to a consensus to consider PLD in the context of >10 cysts.[2,3] PLD occurs in the setting of two distinct hereditary disorders, either as a primary presentation of ADPLD, or associated with polycystic kidneys in autosomal dominant polycystic kidney disease (ADPKD).[1] It is important to differentiate ADPLD from ADPKD because their follow-up, counselling, family screening and prognosis differ. Patients with ADPKD are often counselled by nephrologists as renal cysts in ADPKD may lead to hypertension and end-stage renal disease. Therefore, blood pressure and renal function need to be monitored. While liver architecture is affected by PLD, the synthetic function of polycys-tic liver remains intact until very late in the course of disease. In 2015, an international expert guideline (KDIGO) was published on the management of ADPKD.[4] However, no such guidelines exist for ADPLD. In this review we aim to provide guidance on the care of patients with PLD in relation to key recent developments in the field. Most of our recommendations are based on published scientific research. To provide a complete overview of PLD, some recommendations are based on extensive knowledge gained from working in an expert PLD centre.

What causes the development of liver cysts?

PLD results from germline mutations in *PKD1* or *PKD2* in ADPKD, or *PRKCSH, SEC63, LRP5* in ADPLD.[5,6] Recently, *GANAB* mutations have been discovered in patients with ADPKD and ADPLD, and *ALG8* and *SEC61B* mutations have been exclusively assigned to ADPLD (Fig. 1A).[7] *PKD1* and *PKD2* encode two ciliary proteins, polycystin-1 (PC1) and polycystin-2 (PC2). The latter is also

Grand Rounds

Key point

PLD is a genetically heterogenic disease. Polycystin-1 is postulated to be the key player in liver cystogenesis.

located in the endoplasmic reticulum (ER). PC1 acts as a mechanosensor and PC2 as a calcium channel.[8] Together, these coupled proteins regulate intracellular calcium levels. ADPLD-associated genes, with the exception of *LRP5*, are part of the ER-related glycoprotein quality control mechanism. *ALG8* is important for the correct assembly of glycans that are assembled with precursor glycoproteins in the ER.[9] Co-translational and post-translational translocation of pre-cursor glycoproteins are facilitated by the heteromeric SEC complex, that consists of *SEC61B* and *SEC63* gene products, among others.[10] *GANAB* and *PRKCSH* encode the catalytic α-subunit and regulatory β-subunit of glucosidase II, respectively, and are located downstream of the SEC translocon. Two-step hydrolysis of glycoproteins by glucosidase II is important for their correct folding. *LRP5* is located on the cell membrane where it interacts with Frizzled. Upon binding of Wnt to the Frizzled/LRP complex, the canonical Wnt/β-catenin pathway and subsequent cell proliferative pathways are activated.[11]

Heterozygous mutations do not directly lead to the development of cysts. It is presumed that somatic mutations and, consequently, loss of heterozygosity of the wild-type allele from the cyst epithelium, is needed for PLD to develop.[12] Therefore, a two-hit model has been postulated, inferring that a somatic mutation (second hit) against the backdrop of the germline mutation (first hit) is necessary to initiate cyst development (Fig. 1B). Similar to ADPKD, some patients with ADPLD may develop additional somatic mutations in other genes (transheterozygosity) that are part of the PLD network. It can be hypothesised that the mutation in the second gene initiates cyst development.[13] This theory does not explain the liver specificity of the disease.

PC1 deficiency is the common theme in liver cystogenesis irrespective of the genetic cause.[14] Mutations in ER-related genes lead to aberrant PC1 expression and localisation, resulting in decreased intracellular calcium levels and subsequent cAMP-activation and cell proliferation (Fig. 1B).[8] In addition, PC1 has been implicated in canonical and non-canonical Wnt-signalling pathways, providing a potential link between *LRP5* mutations, PC1 and liver cystogenesis.[15]

Is genetic testing and genetic counselling recommended?

Patients with PLD often ask whether they, but also children and additional family members, should be screened for the presence of causative mutations. For the attending physician, knowledge of the mutation should further contribute to care for this patient. The patient should be informed of the consequences of genetic testing on insurance, employment and the psychological impact, especially on children or asymptomatic family members.

In the majority of patients with ADPKD, the underlying *PKD1*/*PKD2* mutation can be detected with current techniques. Patients with *PKD1* mutations, particularly those with truncating mutations have a more severe renal phenotype, greater number of cysts, larger kidneys and earlier progression to end-stage renal disease compared to those with *PKD2* mutations.[16,17]

Despite an evident relationship between *PKD1*/*PKD2* genotype and the renal phenotype, no evident genotype–phenotype association has been identified pertaining to the hepatic phenotype in PLD.[17,18] Patients with ADPLD have larger volume and greater number of hepatic cysts than patients with ADPKD.[19] The frequency and severity of PLD is higher among patients with *PRKCSH* or *SEC63* mutations.[20] These patients are younger when diagnosed and 95% of mutation carriers suffer from clinical symptoms, compared to ~70% of patients with ADPLD, in whom no mutation could be detected by current techniques. However, a clear relationship between the number of cysts and presence of symptoms has not been proven.[20]

Clinical heterogeneity among patients with ADPLD may be partially explained by the different effects of each mutation on PC1 expression/function,[7] as well as on other proteins that contribute to the process of cystogenesis.[21,22] There is experimental evidence suggesting that knockout of one of the ER-associated genes results in decreased expression of other membrane proteins, such as the Na$^+$/K$^+$-ATPase α1 subunit.[23] This suggests that the mutations may affect other, unidentified proteins, that contribute to the heterogeneous spectrum of liver phenotypes.

The KDIGO guideline suggests that genetic testing is not required for the diagnosis of ADPKD, with the exception of equivocal or atypical renal imaging findings (early and severe PKD, markedly asymmetric PKD, renal failure without significant kidney enlargement, marked discordant disease within family) and sporadic PKD without family history.[24] The clinical diagnosis of ADPKD and ADPLD is established through renal/hepatic imaging analysis. However, genetic testing and genetic counselling might be considered for various reasons: i) Early and precise molecular diagnosis of ADPKD for appropriate clinical management. Accurate diagnose is important, especially since Tolvaptan (vasopressin V(2)-receptor antagonist) is approved for the management of patients with ADPKD and severe disease progression, in order to slow progression to renal failure.[25] Furthermore, genetic testing differentiates between other pathogenic variants associated with renal cysts, such as *HNF1B,* which leads to renal cysts and diabetes mellitus and requires a different treatment strategy;[26] ii) Testing for *PKD1* and *PKD2* mutations contributes to prediction of the prognosis in truncating and non-truncating variants in *PKD1* and pathogenic variants in *PKD2*;[24] iii) Pre-

Key point

PLD is an autosomal dominant disease that is recessive on a cellular level. A somatic mutation on the wild-type allele or a mutation on a second PLD-associated gene is necessary to initiate cyst development.
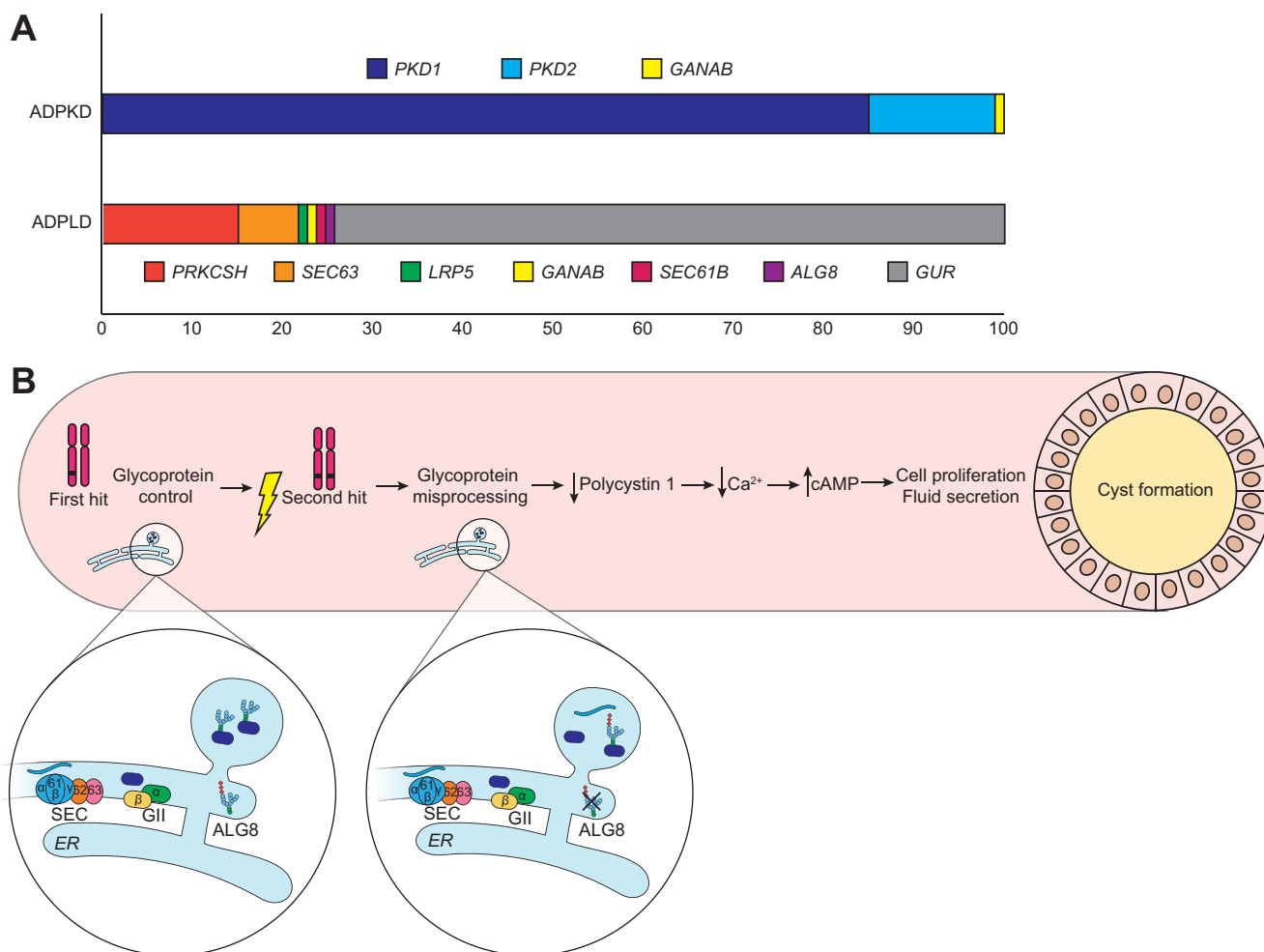
Fig. 1. Molecular background of PLD. (A) Overview of genetic distribution of ADPKD and ADPLD. Each colour represents the percentage of patients with a specific germline mutation. (B) Proposed mechanism of liver cyst formation. PLD patients with a germline mutation acquire a second mutation in the wild-type allele (second hit) that results in deficient glycoprotein assembly and control, and subsequent decrease of polycystin-1 expression. The concurrent decrease in calcium influx leads to increased levels of cAMP and cyst formation through cell proliferation and fluid secretion. ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; cAMP, cyclic adenosine monophosphate; ER, endoplasmic reticulum; GII, Glucosidase II; GUR, Genetically unresolved; PLD, polycystic liver disease.

dictive testing for asymptomatic at-risk adults or at-risk relatives for ADPKD. Patients and relatives are more often in need of certainty about the diagnosis. In patients hoping for a child, genetic counselling can provide information on inheritance patterns and associated recurrence risks, as well as options for genetic diagnosis and pregnancy management.[27]

No guidelines exist for molecular genetic testing and genetic counselling in patients with ADPLD. Identification of the pathogenic mutations underlying PLD does not influence individual clinical management, but adds to a better understanding of disease pathogenesis and paves the way for development of new therapeutic options. However, as discussed above, some patients or family members may need certainty and desire genetic testing and/or counselling concerning risk assessment, management advice and/or family planning.

In conclusion, radiological imaging is the first means to diagnose ADPKD or ADPLD in at-risk individuals or asymptomatic first-degree relatives. Referral for genetic counselling should be considered, especially in patients with ADPKD, permitting an informed choice about diagnosis and screening.

What is the natural course of PLD and what can patients do to stop liver cyst growth?

There is a large variation in the severity of liver disease in PLD. The phenotype of patients who share the same genetic mutation may range from normal liver with only few cysts to incapacitating disease with severe hepatomegaly. Family studies suggest that the disease penetrance is ~80%, so ~20% of mutation carriers will have only mild or absent disease.[28,29] The patients that require our attention are those with moderate to severe hepatomegaly. Many of these patients come to our attention in their thirties and report that they noticed a sudden and accelerated increase of

Key point

Genetic testing and counselling should be considered in patients with ADPKD. Genetic testing in ADPLD needs further investigation, however to date it does not influence individual clinical management, but it adds to a better understanding of disease pathogenesis and development of new therapeutic options.

abdominal girth, superimposed with symptoms related to PLD. The natural history of the disease prior to presentation is unknown, but anecdotal evidence suggests that liver cysts can be detected on ultrasound imaging years before development of associated symptoms.

Several risk factors or patient characteristics for disease severity have been identified through cross-sectional studies. A cohort study in patients with ADPKD and preserved renal function demonstrated that the prevalence and size of liver cysts increased with age. In the fourth decade, 94% of all patients with ADPKD will possess one or more liver cysts.[30] Gender is clearly associated with the severity of disease. Female patients populate >80% of large cohort studies of symptomatic patients with PLD.[20] This mirrors the finding that the large majority (>80%) of patients with PLD who receive liver transplantation are female.[31] This is probably because the disease progresses much faster in females. A pooled analysis of three controlled trials indicated that the liver volume in PLD increases by 1.8% within 6–12 months. Young women (<48 years) have been identified as rapid progressors and have much larger increases in liver volume (+4.8%) compared to older women (+0.6%) or men (−0.1%).[32] Similar results have been found in other larger cohort studies.[17] These gender-dependent differences may be explained by the hormonal status of women. Massive hepatomegaly in women with ADPKD is more common in women with prior pregnancy. A cohort study found that number and size of hepatic cysts in ADPKD correlates with the number of pregnancies. Other studies have drawn an association between oestrogen and liver size in PLD.[33,34] The effect of oestrogen treatment on PLD has been tested in a controlled clinical trial in 19 postmenopausal women with ADPKD. One-year treatment led to selective liver growth (oestrogen +7%, control −2%), but not kidney enlargement.[33] Two recent large retrospective studies did not establish an association between oestrogen use and liver size.[17,35] In the last decades, the dosage of oestrogen in oral contraceptives has been considerably decreased from over 100 mcg to less than 30 mcg.[36] This could explain the contradictory results between the older and more recent studies. The effect size of the association between oestrogen use and natural liver growth needs to be further explored. However, in clinical practice we advise patients to stop taking oral oestrogen containing contraceptives.[37] It is unclear whether an alternative, such as a levonorgestrel-releasing intrauterine device, can be advised, as the effect on liver growth remains to be tested. No other (evidence-based) lifestyle adjustments are known to alter the natural course of PLD.

Clinical presentation and classification

Most patients with PLD will remain asymptomatic through the years, because the number and volume of cysts do not cause substantial hepatomegaly. The development of hepatomegaly heralds abdominal symptoms and prompts imaging studies. Once identified, hepatomegaly resulting from PLD needs to be further categorised in order to assess the severity of disease. The Gigot classification can be used for a crude differentiation between phenotypes. This classification uses the number and size of liver cysts, as well as the extent of liver parenchyma involvement, to categorise patients (Fig. 2).[38] This classification depends on imaging studies, does not include symptoms and is inappropriate for evaluating progression of the disease. A classification that incorporates symptoms does not exist and recent efforts have led to the development of patient-related outcome measures, to gauge disease severity and to monitor disease progression.

PLD-specific questionnaires

Two PLD-specific questionnaires have been developed and validated to capture PLD-related symptoms (e.g. abdominal pain, loss of appetite, early satiety, nausea); POLCA (PLD complaint-specific assessment) and PLD-Q (PLD questionnaire).[39,40] After completion, the total score is calculated by adding individual symptom scores, and a higher total score corresponds with a higher disease burden. Patients were involved in the development of PLD-Q, contrary to the development of POLCA, leading to a different set of items. POLCA was criticised because of its validation process,[41,42] as pretesting of the questionnaire in patients with symptomatic PLD had not been done.[40] However, both questionnaires can be used to score the burden of disease and to assess the changes in symptom burden after treatment. Since treatment is only recommended in symptomatic patients with hepatomegaly, both instruments may serve as new clinical endpoints.

Liver volume

Liver volume is a prognostic marker and the main endpoint for exploring the merits of novel therapeutic strategies, as it impacts both symptom burden and quality of life. CT or MRI volumetry using (semi-) automatic software is used to measure liver volume.[43,44] There are two classifications available that distinguish mild, moderate and severe phenotypes based on htTLV.[35,45] Both classifications use arbitrarily divided classes with different cut-off values for the sub-phenotypes. In our experience, the classification described by Kim corresponds best with reported symptoms and need for therapy. Patient disease severity is classified as mild (htTLV <1,600 ml), moderate (htTLV 1,600–3,200 ml/m) and severe (htTLV >3,200 ml/m) (Fig. 2).[45] In the following section we provide guidance on how to make a quick estimation of liver volume and disease severity, based on current literature and our own experience. It is important to realise that the shape of the liver in

Key point

Age and gender are risk factors for disease severity. The association between severity and oestrogen use needs to be further elucidated.

Fig. 2. Mild, moderate and severe phenotype according to the classification used by Kim.[45] In all three images the liver is accentuated; cysts are coloured dark, whereas the lighter parts resemble normal liver parenchyma. (A) Coronal CT image (with contrast) with three-dimensional view of *mild* phenotype (htTLV 1380 ml/m) showing multiple medium-sized cysts with large areas of non-cystic liver parenchyma (Gigot Type II). (B) Coronal CT image (no contrast) with three-dimensional view of *moderate* phenotype (htTLV 2,773 ml/m) showing multiple cysts diffusely through the liver and only a few areas of normal liver parenchyma between cysts (Gigot Type III). (C) Coronal CT image (no contrast) with three-dimensional view of *severe* phenotype (htTLV 5,065 ml/m) showing multiple cysts diffusely through the liver and only a few areas of normal liver parenchyma between cysts (Gigot Type III). Note: Gigot type I (patients with a limited number (<10) of large cysts (>10 cm)) does not meet the definition for PLD. Normal liver volume 1,300–1,700 ml, htTLV approximately 700–1,000 ml/m. CT, computed tomography; htTLV, height-adjusted total liver volume; PLD, polycystic liver disease.

PLD varies greatly among patients, even in those with similar liver volumes.

Mild PLD

Patients with mild PLD (Fig. 2A) rarely develop symptoms or complications and might not seek care unless liver cysts are incidentally found on radiological imaging, as happened in our case presentation. This may lead to an underestimation of the prevalence. In 1986, an autopsy study estimated the overall prevalence to be 1 per 200.[46] Many patients will never realise that they are affected unless PLD is detected as an incidental finding on abdominal imaging. The minority of patients with mild PLD who develop symptoms may suffer from pain located to the back and flank.[45] Sometimes this pain is caused by a large dominant cyst that stretches the liver capsule. As depicted (Fig. 2A), organ compression does not occur in mild PLD and abdominal girth is not increased. Routine surveillance of asymptomatic patients is not recommended.

Moderate PLD

Patients with an htTLV exceeding 1,600 ml/m run a higher risk of pressure-related symptoms.[45] The effects of the enlarged liver on the stomach, lungs and intestines may cause symptoms such as pain in the abdomen, flank or back, early satiety, nausea, bloating, gastro-oesophageal reflux, and dyspnoea. These symptoms significantly decrease quality of life.[47] In most patients with moderate PLD, the liver reaches the left flank of the body and is palpable below the costal margin (Fig. 2B). Often, the right kidney migrates caudally because of increased liver mass.

Severe PLD

Typically, patients with severe PLD are female and aged between 30 and 50 years. Compression of the stomach may cause early satiety, decreased food intake and result in weight loss and sarcopenia. We advise patients to spread their meals into multiple, smaller portions over the day. In severe PLD, the right hepatic lobe extends into the pelvis and upon clinical examination the lower rim of the liver is clearly palpable. As a result of the liver being caudally displaced, the ribcage becomes distended because of an elevated (hemi-) diaphragm (Fig. 2D). Irrespective of liver volume, the function of the liver remains preserved. However, recent findings suggest that compression of hepatic veins (or inferior vena cava [IVC]) causes hepatic venous outflow obstruction (HVOO). This is present in 92% of patients who underwent liver resection or liver transplantation. The exact clinical impact is unclear, but HVOO is associated with postoperative ascites and liver failure. Furthermore, histological examination will reveal liver fibrosis in 56.8% of patients.[48] Elevated alkaline phosphatase (47%) and gamma-glutamyltransferase (70%) levels can be seen in moderate to severe disease and do not bear clinical significance.[49]

A protruding abdomen may cause psychological problems. Although no significant effect of disease stage on mental status has been demonstrated,[35] we regularly see severely affected young female patients with psychosocial complaints. Considerable bulging of the abdomen may suggest full-term pregnancy, which leads to incorrect assumptions and uncomfortable confrontations with others. The impact on mental quality of life remains to be fully elucidated in

Key point

Staging of PLD is complex, as a classification with clinical important endpoints is lacking. PLD-specific questionnaires (PLD-Q and POLCA) and liver volume are essential to estimate disease severity in clinical practice, monitor progress of the disease, and measure treatment effect.
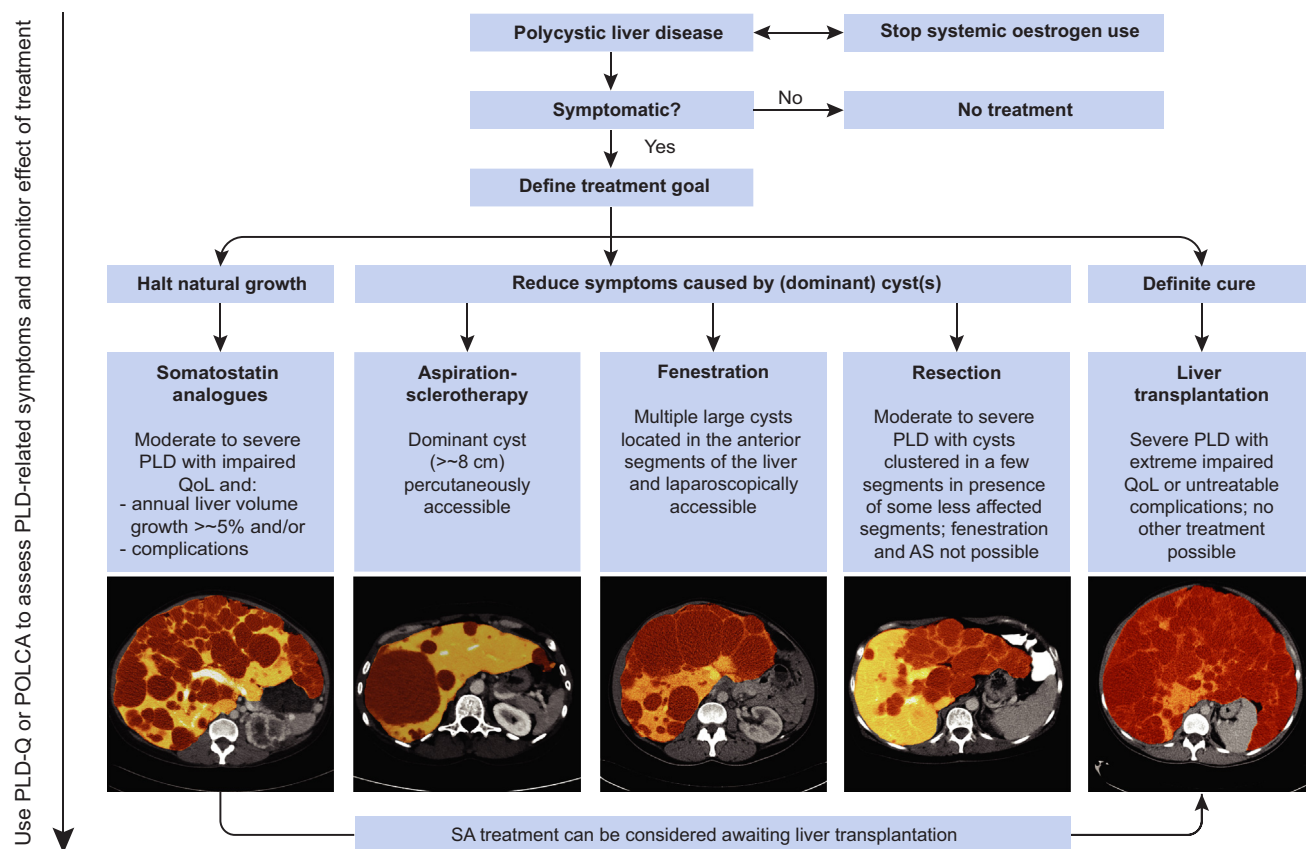
Fig. 3. Treatment algorithm for polycystic liver disease subdivided by treatment goal. Treatment is only indicated in symptomatic patients and choice of treatment depends on expertise and availability in the local centre. The transversal CT images serve to show the phenotype applicable to each type of treatment. The liver is accentuated; cysts are coloured dark whereas the lighter parts resemble normal liver parenchyma. AS, aspiration sclerotherapy; CT, computed tomography; PLD, polycystic liver disease; QoL, quality of life; SA, somatostatin analogues.

patients with the most severe phenotype (*e.g.* htTLV >3,500 ml/m).

As patients with moderate or severe phenotype are at risk of developing symptoms or requiring future therapy, they should be referred to expertise centres to receive counselling and appropriate interventions.

Which complications may occur during the course of PLD?

Complications in PLD can be divided into two categories: intra-cystic complications and liver volume-related complications. These complications are listed below in the order of frequency that we encounter them in our clinical practice.

Intra-cystic complications
Hepatic cyst haemorrhage
Cyst haemorrhage predominantly occurs in a large solitary cyst (mean size 11 cm) and may manifest with acute pain in the upper abdomen or flank.[50] In clinical practice, signs of elapsed cystic haemorrhage are regularly seen on ultrasound in patients without any history of preceding symptoms, suggesting that cystic haemorrhage frequently occurs asymptomatically and is probably underreported. The exact incidence is unknown. High intra-

cystic pressure, rapid growth of the cyst or direct trauma are presumed triggers for this complication. Cyst haemorrhage results in internal inhomogeneity due to fibrin wires and clots, and higher Hounsfield units (HU) at radiological imaging (0–20 HU in uncomplicated liver cyst).[51,52] Because of imaging similarities with liver neoplasms on ultrasound, it can be a challenge to differentiate between a benign cyst with internal haemorrhage or a biliary cystadenoma or cystadenocarcinoma.[50] Differentiation is possible with CT or MRI, haemorrhagic cysts show no contrast enhancement in septa and the capsule of the lesion.[53] In the case of mild symptomatic cystic haemorrhage, conservative treatment is advised. In severe symptomatic cases with non-regressive pain, deroofing of the cyst or enucleation can be considered.[50]

Hepatic cyst infection
Hepatic cyst infection (HCI) is characterised by the combination of pain in the right upper quadrant, malaise and fever.[1] Without treatment, sepsis and death may ensue. There is no association between liver volume and occurrence of HCI.[45] The identification of inflammatory cells and bacteria from cyst aspirate is considered the gold standard for diagnosis of HCI. If a cyst aspirate is

unavailable, a combination of clinical and biochemical parameters can be used.[54] [18F] Fluorodeoxyglucose-positron emission tomography (FDG-PET) allows identification of FDG accumulation in epithelia of infected cysts and may be used to confirm the diagnosis and to differentiate between hepatic or renal cyst infection. The diagnostic properties of FDG-PET are incomplete, as anecdotal evidence suggests that FDG accumulation only occurs in a late stage of the disease, and that FDG accumulation may disappear despite the presence of a well-established infection.[55] HCI incidence has been estimated at 1% of all patients with hepatic cysts.[56] Most liver cyst infections are thought to arise from translocation of bacteria across the intestinal barrier. *Escherichia coli* and *Klebsiella* species are the most common microbial organisms isolated from blood cultures or cyst aspirates.[57] Antibiotic treatment is guided by culture and aspirate results and is recommended as first line therapy. However, in 64% of patients, monotherapy with antibiotics does not result in complete remission of the infection. In case of antibiotic failure, cyst drainage should be considered.[54] FDG-PET can be used in combination with serum C-reactive protein to evaluate treatment effect.[55]

Hepatic cyst rupture

Rupture of a cyst is rare enough to merit publication in case-reports. A rupture is associated with a substantial increase of cyst volume, caused by haemorrhage, trauma or spontaneously. This increase in cyst volume reduces the stability of the cyst wall. Severe abdominal pain is the most typical symptom. Radiological imaging shows free fluid around the liver and often a residual cyst in the liver. If possible, a conservative strategy is warranted, but in some cases patients present with acute abdominal pain and haemodynamic instability. Without early recognition and treatment this complication can be fatal. Treatment consists of percutaneous drainage of ascites and liver cysts or surgical intervention.[56,58]

Liver volume-related complications

Complications resulting from pressure on adjacent organs by a single cyst or by the enlarged liver are rare, but may be severe depending on the location. The incidence of such complications is unknown. Moderate to severe PLD (htTLV >1,600 ml/m) and female gender are associated with a higher risk of pressure-related complications.[45] Several case-reports illustrate the development of obstructive jaundice, portal vein occlusion, portal hypertension with splenic varices, Budd-Chiari Syndrome, and compression of the IVC leading to peripheral oedema and ascites in PLD. To date, no consensus exists regarding treatment strategies for each type of complication, but individualised treatment is highly recommended.[59] In patients with symptomatic ascites and compression of the IVC who are not responding to medical therapy, stenting of IVC may be considered. A retrospective cohort demonstrated that this intervention is safe and effective, and decreases pressure in IVC, resulting in improved clinical symptoms and diuretic requirements.[60]

Which treatment options are currently available?

In patients with symptomatic PLD and hepatomegaly there is an unmet need for treatment. A key issue in the management of PLD is defining one common goal with the patient. These goals may include a lower liver volume, but also a better quality of life and/or reduction of symptoms. Whether therapy should be finite and the time frame in which goals should be achieved must also be defined. The available radiological, surgical and pharmacological treatment options reflect different treatment goals (Fig. 3). The next section summarises the available therapies categorised by each treatment goal.

Patient: 'I want my liver to stop growing'

Somatostatin analogues (SAs) are the only medical therapy that alter the natural course of PLD. Cystic fluid secretion and cell proliferation are driven by the hyper production of cAMP. Somatostatin, a natural occurring hormone in the gastrointestinal tract, inhibits the production of cAMP in cystic cholangiocytes, leading to decreased fluid secretion and proliferation. Almost a decade ago, the first clinical trial demonstrated that SAs reduce liver volume in PLD. This randomised controlled trial assigned patients with PLD to injections every four weeks with a long-acting SA (lanreotide 120 mg) or placebo. Six months of lanreotide injections decreased liver volume by 2.9%, whereas those on placebo increased liver volume by 1.6%.[61] Continuation of the drug for another six months resulted in stabilisation of liver volume.[62] Several other trials confirmed that both long-acting lanreotide and octreotide decrease liver volume.[32] All results from SA trials are based on a treatment period between six months and three years. Further research is needed to explore the effect of long-term maintenance therapy. Treatment with SAs improves quality of life in symptomatic patients with PLD.[63] A pooled individual data analysis indicates that patients with both APDKD and ADPLD benefit from SAs and this effect is not influenced by baseline liver size. Young women benefit most from SA treatment, probably because they have the largest natural liver growth.[32] Several (transient) side effects may occur (*i.e.* abdominal discomfort, diarrhoea, pale stools, gallbladder stones), but in general SA treatment is well tolerated and considered safe.[21,64] Due to the high

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Key point

In patients with symptomatic PLD and hepatomegaly there is an unmet need for treatment. Choice of treatment is dependent on therapeutic goal, cyst distribution (location and size), local expertise, and availability.

Key point

Treatment with somatostatin analogues is the most effective pharmaceutical option as it decreases liver volume and improves quality of life. Future research should focus on combination therapy with SA and other drugs to seek a synergistic effect.

costs, this treatment is reserved for symptomatic patients with moderate to severe disease and reduced quality of life, where referral to a specialised centre is recommended.

Patient: 'I want to get rid of my complaints caused by one or more dominant cysts'

Aspiration sclerotherapy

Patients with symptoms caused by one dominant cyst are eligible for aspiration sclerotherapy (AS). In most cases a threshold cyst diameter of ∼5 cm is used.[65] The aim of this minimally invasive treatment is to reduce the cyst volume by puncturing the cyst with radiological guidance.[66] After aspiration of cyst fluid, the cyst is temporarily exposed to a sclerosing agent in order to destroy the inner epithelial lining. This procedure is safe and shows high clinical and technical efficacy rates. In one study, reduction of symptoms was seen in 72% of patients with PLD, 59% of whom had complete resolution, compared to patients with solitary cysts, in whom 94% had reduced symptoms and 82% complete resolution.[66] The most frequently reported side effects are post-procedural pain (range 5–90%) and hepatic cyst bleeding (range 2–23%), no mortality has been reported.[66]

Fenestration

Cyst fenestration should be considered in patients who experience symptoms due to multiple larger cysts, on the condition that these cysts are accessible, and preferably located in the anterior segments of the liver.[67,68] Cyst fenestration combines aspiration and surgical deroofing of liver cysts.[69] The advantage of this procedure, compared to AS, is that multiple cysts can be treated in one session. Instant symptom relief after the procedure is achieved in 92% of the patients, but recurrence of symptoms (22%) and re-accumulation of cyst fluid (24%) occurs.[65] A laparoscopic approach is the current state of the art and results in a shorter hospital stay and lower complication rates than an open approach. Complications are not infrequent (23%) and include postoperative ascites, pleural effusion, and bleeding. Mortality occurs in 2% of all procedures.[65] A randomised controlled trial comparing safety and efficacy of cyst fenestration and AS has not yet been conducted. The choice between both techniques is mainly based on patient phenotype and local experience.[3]

Resection

When AS or fenestration is not possible because of unfavourable distribution of the cysts, segmental hepatic resection may be considered. This procedure is warranted in cases of symptomatic and severe hepatomegaly, in which few liver segments have multiple cysts, but other segments are less affected.[70,71] In some cases, dual therapy with segmental resection and fenestration of less affected segments can be performed.[69] Although partial hepatectomy significantly decreases liver volume, by a median of 61% in one study, peri-operative risks are significant.[72] Mortality rate after dual therapy was 2.7% and major therapy-related complications occured in 21% of the patients leading to a total morbidity rate of 21–51%.[72] Evidence suggests that major surgery, such as partial hepatectomy, complicates future liver transplantation because of a high occurrence of post-procedural adhesions.[73,74] Hepatic resection may be considered as on option for the phenotype outlined above, but given the high morbidity and mortality rate, it should only be performed in centres with experience and expertise to reduce the risk of complications.

Patient: 'I want to be cured!'

Liver transplantation

Liver transplantation is the only curative treatment option, but only a minority of patients with PLD will qualify for this intervention. Patients with massive hepatomegaly who suffer from severe malnutrition, low serum albumin, sarcopenia or severe and recurrent complications such as cyst infections or portal hypertension, should be referred, so that liver transplantation can be considered.[75] In liver diseases, the MELD score, used to assess three-month prognosis in patients with liver failure, is a leading instrument to select patients for liver transplantation. As the function of the liver in patients with PLD remains intact, this score will not increase. To gain priority, exception guidelines are used that allow patients with PLD to earn exception points after a certain time on the waiting list.[76] Data from the European Liver Transplantation Registry show that the five-year graft survival and patient survival rate is 87.5% and 92.3%, respectively.[31] Previous open PLD surgery results in higher mortality rates (five-year patient survival 48%) whereas previous minimal invasive disease-related surgery does not.[74] Considering the complexity of this major surgery, morbidity and mortality risks, and the limited availability of donor livers, this option still has a limited place in the choice of therapy in patients with PLD. Combined liver-kidney transplantation in patients with ADPKD and severe renal impairment should be considered, as evidence shows that it is associated with better outcomes (patient and graft survival) compared to liver transplantation alone.[77] We suggest a multidisciplinary approach involving hepatologists and nephrologists for this group of patients.

If a patient needs therapy, we advise discussing treatment options with an expert in the field of PLD. Once a certain intervention is chosen we recommend referring the patient to an expert centre with extensive experience of the suggested intervention, to reduce the chance of morbidity and mortality.

What other potential new and effective therapies will be available in the near future?

Since PLD is a disease with great genetic heterogeneity and multiple factors influence the development and progression of disease, a monotherapeutic approach may be inadequate to address all pathways involved. SAs are currently our most effective pharmaceutical options. Therefore, we believe future research should explore SAs combined with other drugs to look for a synergistic effect. The combination of octreotide and mTOR inhibitor everolimus for 48 weeks did not show a significant additive effect compared to octreotide alone.[78]

Modification of the bile acid pool and targeting bile acid receptors may be the focus of future combination therapies. Bile acids have been identified as signalling molecules that are involved in multiple processes including cell proliferation, liver regeneration and programmed cell death. In particular, the PCK rat, an animal model of PLD, is characterised by increased hepatic accumulation of toxic bile acids, which promote cystic cholangiocyte growth. Similarly, increased bile acid concentration is present in PLD cystic fluid.[79] Of note, chronic administration of the choleretic ursodeoxycholic acid (UDCA) to PCK rats, with the aim of increasing intracellular calcium levels in cystic cholangiocytes and reducing the high concentration of toxic bile acids in the liver, inhibited hepatic cystogenesis.[79] A phase II randomised clinical trial did not support its efficacy, though a *post hoc* analysis showed a beneficial effect of UDCA on liver cyst volume growth in ADPKD.[80]

TGR5 is a G protein-coupled bile acid receptor located in the apical membrane and primary cilium of cholangiocytes. Activation of TGR5 increases cAMP levels and biliary chloride secretion.[81] TGR5 is overexpressed in PCK livers and stimulation of the receptor *in vitro* results in increased cAMP levels, cell proliferation, and cyst growth. *In vivo*, the TGR5 agonist, oleanolic acid, worsened hepatic cystogenesis, whereas *TGR5* knockout reduced cyst growth. The TGR5 antagonist SBI-115, a novel small molecule, decreases cAMP levels, cell proliferation and cyst expansion in cystic cholangiocytes. This effect could be further enhanced by concurrent administration with the SA, pasireotide.[82] Thus, the use of TGR5 antagonists could be a new therapeutic strategy that deserves further attention.

Back to the clinical vignette

Our patient suffers from severe PLD. Her htTLV increased by 1,380 ml/m (51.7%) over the last five years, translating into an annual growth rate of 8.7%. We expected that with conservative management we would see a further increase of liver volume. This put her at risk of developing mass-related symptoms, such as impaired food intake, with ensuing weight loss and sarcopenia. Upon review of her imaging studies we could not identify a dominant cyst responsible for her symptoms. For this reason, aspiration was not an option. The cysts were evenly distributed in all segments of the liver which ruled out fenestration and resection. The burden of disease was high (PLD-Q score 65/100) and her condition had a significant impact on her daily life, but she told us that she had learned how to cope with the impact of the disease. She was worried that her liver would continue to expand and feared the impact of the disease on her daily life. We decided to start treatment with SA and she received lanreotide 120 mg subcutaneously every 28 days for 18 months. After 18 months, htTLV had decreased from 4,047 ml/m to 3,825 ml/m (−3.7% per year) and PLD-Q score improved to 46/100. In conclusion, with this therapy we were able to alter natural liver growth, and improve nutritional status and general well-being. Because of this positive effect, we decided to continue SA therapy. Whether the effect of SA will be maintained is uncertain, as studies show that the largest effect size is achieved in the first months. If therapy fails and symptoms recur in the next treatment period, surgical options such as liver transplantation will be explored.

Conflict of interest

R.M.M. van Aerts, L.F.M. van de Laarschot and J.M. Banales declare no competing interest. J.P.H. Drenth declares associations with the following organizations/companies: Ipsen, Novartis.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

RvA, LvdL and JD drafted and designed this manuscript. RvA and LvdL wrote this manuscript with support from JD and JB. All authors read and approved the final manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2017.11.024.

Grand Rounds

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