Grand Rounds

JOURNAL OF HEPATOLOGY

Clinical management of polycystic liver disease☆

René M.M. van Aerts[1], Liyanne F.M. van de Laarschot[1], Jesus M. Banales[2], Joost P.H. Drenth[1,*]

Summary

In this Grand Rounds article, we present a typical case of a woman with polycystic liver disease. This case prompts questions which both patients and clinicians may face in clinical practice. This article aims to provide guidance to clinicians caring for patients with polycystic liver disease, in relation to key recent developments in the field. We discuss the latest advances in our understanding of pathophysiology, the natural course of disease, complications, as well as existing and potential new treatment options.

Keywords: Polycystic liver disease; Liver cysts; Clinical management; Liver volume; Quality of life; PLD-Q; POLCA; Complications; Treatment.

Received 30 June 2017; received in revised form 20 September 2017; accepted 18 November 2017

[1]*Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands*
[2]*Department of Liver and Gastrointestinal Diseases, Biodonostia Research Institute – Donostia University Hospital, University of the Basque Country (UPV/EHU), IKERBASQUE, CIBERehd, San Sebastián, Spain*

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?

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 polycystic 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

☆ The Radboudumc Department of Gastroenterology and Hepatology is part of ERN-rare liver http://www.rare-liver.eu/.

* Corresponding author. Address: Department of Gastroenterology and Hepatology, Radboud University Medical Center Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 361 9190; fax: +31 24 363 5129.
E-mail address: joostphdrenth@cs.com (J.P.H. Drenth).

Please cite this article in press as: van Aerts RMM et al. Clinical management of polycystic liver disease. J Hepatol (2018), https://doi.org/10.1016/j.jhep.2017.11.024

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?

Key point

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

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 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]

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.

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

Please cite this article in press as: van Aerts RMM et al. Clinical management of polycystic liver disease. J Hepatol (2018), https://doi.org/10.1016/j.jhep.2017.11.024