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REVIEW

Hepatic and renal manifestations in autosomal dominant polycystic kidney disease: a dichotomy of two ends of a spectrum

J.J.M. van Gulick, T.J.G. Gevers, L. van Keimpema, J.P.H. Drenth*

Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-3614760, fax: +31 (0)24-3540103, e-mail: joostphdrenth@cs.com

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder. It is the most common genetic cause of end-stage renal disease. One frequent extra-renal manifestation is hepatic cyst formation. The majority of ADPKD patients develop complications as a result of renal cyst formation; however, a small proportion develop extensive hepatic disease with minor renal features. Both phenotypes seem to represent the spectrum of ADPKD. This review discusses the current understanding of the pathogenesis of the disease, its manifestations and the mechanisms of cyst formation. Furthermore, it focuses on monitoring the disease and the treatment options currently available.

KEYWORDS

ADPKD, hepatic phenotype, polycystic liver, diagnosis, treatment

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of end-stage renal disease.[1,2] It is a multisystem disorder and the primary phenotype is characterised by renal cyst growth causing enlargement of the kidneys. The most common extra-renal manifestation is hepatic cyst formation.[3] While the majority of ADPKD patients develop complications secondary to renal polycystic disease, there appears to be a proportion of patients who have limited renal disease but extensive hepatic disease. Both subsets appear to represent the spectrum of ADPKD and require a different approach to diagnosis and management. Most of the topical reviews have focused on the renal aspects of the disease, and less so on the hepatic phenotype. In order to address this issue we provide a detailed overview of the current literature with a focus on both the renal and hepatic phenotype of ADPKD.

RENAL MANIFESTATIONS OF ADPKD

The clinical course of ADPKD is highly variable, partly due to contribution of gene-modifier effects (see textbox). Renal cysts vary in size and appearance and may arise from all segments of the nephron.[4] The formation of cysts leads to the destruction of renal parenchyma and causes renal enlargement, thereby disrupting the normal architecture of the kidney. The initial phase of the disease is often clinically silent.[5] Symptoms arise late in adulthood and are related to the progressive growth of the kidneys, as the size of the kidneys increases from a normal size of 150 to 200 cm^3 to >1500 cm^3 per kidney.[6] Flank pain, haematuria, renal colic, recurrent urinary tract infection and arterial hypertension may be presenting symptoms.

Hypertension is the most common manifestation in ADPKD and is present in about 50% of patients aged 20 to 34 years with normal renal function.[7] Despite the progressive growth of cysts in both kidneys, renal function is well preserved as long as functioning nephrons undergo compensatory hypertrophy.[8] Generally, renal function is maintained until the 4th to 6th decade of life. However, once the compensatory mechanism of the kidneys fails, a rapid decline in renal function occurs. The progressive disease ultimately leads to end-stage renal disease, and chronic renal failure presents in about 50% of patients by the age of 60.[9]

MONITORING PROGRESSION OF RENAL DISEASE

The initial step in diagnosing ADPKD is renal ultrasound. The presence of at least three unilateral or bilateral renal cysts in patients aged 15 to 39 years and of two cysts in each kidney in patients aged 40 to 59 years is sufficient for diagnosis in at-risk individuals from ADPKD families. Four cysts or more in each kidney are required in at-risk individuals aged >60 years.[10] In families with known *PKD1* gene mutation, diagnostic criteria are expressed in number and location of renal cysts related to age.[11]

Monitoring of disease progression in ADPKD differs from other renal diseases. In ADPKD, renal function decreases only late in the course of the disease due to compensatory mechanisms of intact nephrons. In order to prevent this decline in renal function, therapies should be targeted to patients in an early phase of their disease.

The Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) demonstrated that total kidney and cyst volume increase exponentially (± 5% annually), even prior to the loss of kidney function.[6] Moreover, the rapidity of increase of renal volume is associated with a future decline in renal function.[8] Finally, ultrasound is less accurate for determining small changes in renal volume and measuring large kidneys when compared with magnetic resonance imaging (MRI).[12] Although the relationship between kidney volume and renal function may be true for the population at large, individual patients with a high total renal volume may have preserved kidney function.

MANAGEMENT OF RENAL ADPKD

To date there is no treatment available to delay disease progression in patients with ADPKD. Current management recommendations for patients with ADPKD include optimal blood pressure control and sufficient fluid intake. Furthermore, smoking, long-term administration of nephrotoxic agents and probably excessive caffeine intake should be avoided, as caffeine may promote renal cyst growth.[13] However, it remains uncertain whether adequate hypertension management delays renal failure in ADPKD.

In patients with chronic pain refractory to conservative measures, surgical interventions including surgical cyst fenestration or cyst aspiration in combination with injection of sclerosing agents can be considered.[9] Renal transplantation is the treatment of choice for end-stage renal disease in patients with ADPKD. The procedure for renal transplantation for ADPKD differs from most other indications as the native polycystic kidney(s) may necessitate removal due to space constraints secondary to massive renal enlargement.[1,12] Several medical options aimed to slow cyst growth and thereby delay the onset of end-stage renal disease are currently being explored.

Somatostatin analogues are thought to stabilise cyst volumes in ADPKD patients.[13] Indeed, several randomised controlled trials demonstrated a beneficial effect of somatostatin analogues on polycystic kidney volumes in patients with ADPKD.[14,15] However, due to the short duration of trials, the effect on renal function and end-stage renal disease could not be determined. Mammalian target of rapamycin (mTOR) inhibitors are another class of drugs that have been suggested to delay the progression of ADPKD. However, two recent trials using everolimus and sirolimus, both mTOR inhibitors, failed to influence the decline in renal function or to halt polycystic kidney growth.[16,17] Finally, Tolvaptan is a vasopressin V2 receptor antagonist that inhibits renal cyst growth in an animal model for polycystic kidney disease.[18] A prospective, three-year, placebo-controlled trial of Tolvaptan (TEMPO 3-4) is now ongoing to determine whether this drug is safe and effective in delaying the progression of ADPKD.[19]

A DICHOTOMY

The renal phenotype dominates in the largest proportion of ADPKD patients. However, in a subset of patients, hepatic cysts overtake renal cysts and patients suffer more from their polycystic liver. The overall prevalence of hepatic cysts in patients with ADPKD is 83%.[20] The prevalence increases with increasing age and decreasing renal function and is the highest in patients with end-stage renal disease.[1] However, most patients have only a few hepatic cysts and polycystic livers, arbitrarily defined as >20 cysts, occur infrequently.

Indeed, there are a number of risk factors for polycystic livers in ADPKD. Sex appears to be the most defining risk factor; females are more likely to suffer from a polycystic liver.[21] Furthermore, female patients with prior pregnancies and/or use of oestrogens have more and larger liver cysts. In addition, renal cyst volume is correlated with a more severe hepatic disease.[20,22-24] Nonetheless, a proportion of ADPKD patients present both renal cysts and normal renal function but extensive hepatic disease. These patients are not threatened by renal complications of the disease, but clearly develop symptoms secondary to hepatic polycystic disease. Testament to this observation are the cohorts of ADPKD patients recruited for clinical trials that aimed at reduction of liver volume. For example, 32 ADPKD patients with polycystic livers participated in a trial examining lanreotide treatment. These patients showed both an increased average renal volume of 1000

ml (normal 154-202 ml per kidney) and an extensive mean liver volume of 5119 ml (normal 1500 ml) though without renal complications; few of these patients had hypertension, and renal function was normal in most cases.[14] These findings emphasise the importance of a different approach to ADPKD patients with polycystic livers than to ADPKD patients with renal manifestations. This dichotomy of both extensive polycystic kidney disease and few hepatic cysts and extensive hepatic cysts and relatively few renal cysts is illustrated in *figure 1* by panel A, B and C respectively.

HEPATIC MANIFESTATIONS OF ADPKD

Liver cysts arise from cholangiocytes as the result of ductal plate malformation.[25] Several pathways are involved in the growth of hepatic cysts (see *Textbox*). Symptoms are related mainly to liver size, as polycystic livers can grow to up to ten times their normal size. Compression of adjacent abdominal and thoracic organs may lead to abdominal pain, abdominal distention, early satiety, nausea and vomiting.[26] Clinical course and indications for interventions are therefore highly dependent of total liver volume.

MONITORING PROGRESSION OF HEPATIC CYSTS

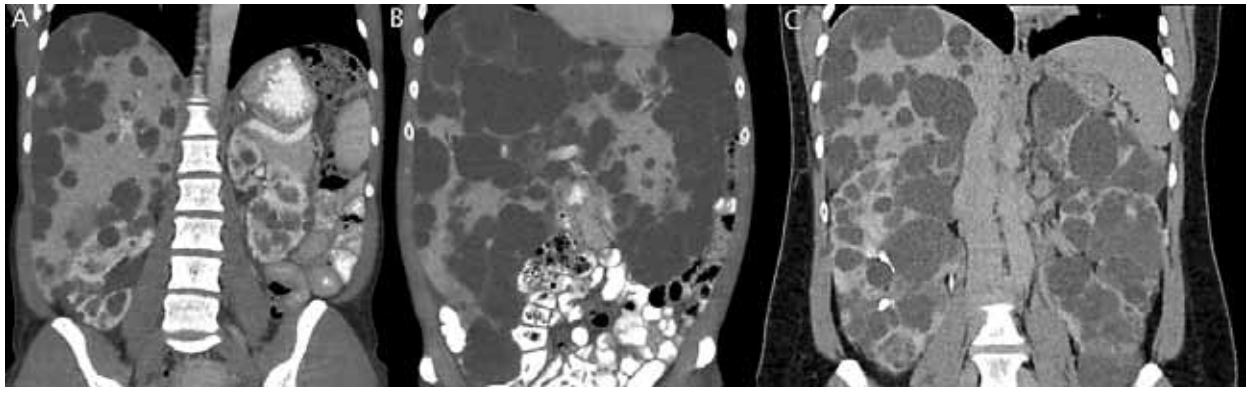
Liver function is generally maintained during the whole course of the disease. Few patients demonstrate abnormalities in liver function or liver enzymes.[27] There are no specific laboratory tests that predict the presence of liver cysts in ADPKD. Hepatic cysts are detected using ultrasound. The CRISP study showed a higher prevalence of hepatic cysts in early ADPKD using MRI compared with ultrasound.[20] The implication of early detection remains unclear, as interventions are currently considered as soon as symptoms develop. Because oestrogens stimulate cholangiocyte proliferation and enhance cyst formation, it is advised to avoid the use of oestrogens.[28] Imaging of hepatic cysts should be guided by symptom management.

TREATMENT OPTIONS FOR HEPATIC CYSTS IN ADPKD

The main indications for treatment of hepatic cysts are abdominal pain, abdominal mass, fullness and early satiety. A variety of surgical and medical options exist for the treatment of hepatic cysts in ADPKD. Among the surgical options are aspiration in combination with sclerotherapy, fenestration, segmental hepatic resection and liver transplantation.[37-44] Aspiration and subsequent sclerosis of hepatic cysts is best performed in a dominant and large, likely symptomatic, cyst. In laparoscopic fenestration multiple cysts are unroofed in one session. Segmental hepatic resection may be considered in cyst rich segments in the presence of at least one predominantly normal segment. All surgical options are invasive, and carry a certain morbidity and mortality risk but provide relatively instant relief. However, recurrence of treated cysts is not infrequent (21 to 39%).[29-34] Liver transplantation is the only curative option and is indicated for severe polycystic livers with extreme disabling symptoms or untreatable complications. Combined liver-kidney transplantation should be considered in patients who are listed for liver transplantation and have an impaired kidney function (GFR <30 ml/min).[36,37]

Current medical options in the treatment of ADPKD are somatostatin analogues and mTOR inhibitors.

Figure 1. *A dichotomy in ADPKD phenotypes. Panel A shows a coronal computed tomography of a patient with ADPKD presenting extensive renal disease and relatively few hepatic cysts. By contrast, panel B and C show a patient with ADPKD presenting extensive hepatic disease and relatively few renal cysts*



PATHOGENESIS IN ADPKD

ADPKD gene mutations

ADPKD is genetically heterogeneous with the responsible genes localised to separate loci on chromosome 16 (*PKD1* gene), accounting for the majority of ADPKD cases (80 to 85%), and chromosome 4 (*PKD2* gene), accounting for 15 to 20% of cases.[42] Patients with a mutation in the *PKD1* gene have significantly more severe renal disease compared with *PKD2* carriers, as *PKD1* gene mutations lead to a 15 to 20 year earlier median age of onset of end-stage renal disease (53.0 *vs* 69.1 years) and larger kidneys.[7]

The pathogenesis of cyst formation is currently thought to involve increased cell proliferation, fluid accumulation and basement membrane remodelling. Various genetic and biochemical pathways contribute to cystogenesis.

Polycystins

PKD1 and *PKD2* encode proteins called polycystin-1 and polycystin-2. While polycystin-1 is a membrane protein localised at sites of cyst formation, including renal tubular epithelia and hepatic bile ductules, polycystin-2 is primarily expressed in the distal tubules, collecting duct and thick ascending limb.

Pathways in cystogenesis

It is thought that increased cell proliferation and apoptosis combined with revascularisation, enhanced fluid secretion and abnormal cell-matrix interactions contribute to cyst formation.[25]

Apart from gene modifier effects, hepatic cysts exhibit higher levels of phosphor-mammalian target of rapamycin (mTOR). This serine/threonine protein kinase, encoded by the FRAP1 gene, regulates cell growth and cell proliferation. Higher levels of mTOR contribute to cholangiocyte proliferation and cyst expansion.[41] Another biochemical mechanism that enhances cyst formation is cAMP activation. ADPKD cells seem to have an altered responsiveness to cAMP stimulating both apical chloride secretion which leads to accumulation of cyst fluid and cell proliferation itself.[43] Furthermore, oestrogens, insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are overexpressed in hepatic cystic epithelium and promote cholangiocyte proliferation in an autocrine way.[44] Although hardly understood and complex, unravelled pathways offer promising targets for therapeutic interventions.

Somatostatin analogues, such as lanreotide and octreotide, are cyclic adenosine monophosphate (cAMP) level inhibitors and decrease fluid secretion and cell proliferation in many cell types, such as cholangiocytes.[14,38-40] The effect of these agents, especially long-acting somatostatin analogues, has been studied in a number of trials in polycystic livers. On the short term (up to 6 and 12 months), these studies show regression of liver volume (-5% to -2.9%), contrasting the increase in the placebo groups (+0.9% to +1.6%).[14,38-40]

mTOR inhibitors are another class of drugs known to inhibit liver cyst growth. In a study performed to optimise the immunosuppressive strategy after renal transplantation, a retrospective measurement of liver volume was performed to elucidate whether sirolimus had any effect on the liver volume.[41] Sirolimus reduced liver volume by 11.9%, whereas tacrolimus caused an increase in liver volume of 14.2%.

In conclusion, somatostatin analogues and probably mTOR inhibitors are the first two identified drug classes that change the natural course of the polycystic disease, although the effect is still limited. Effects of prolonged therapy of somatostatin analogues or mTOR inhibitors on liver volume are still unknown.

CONCLUSION

The majority of ADPKD patients develop complications due to renal polycystic disease; however, a proportion of patients present with extensive hepatic disease and possess only minimal renal features. Both phenotypes of this disease appear to represent either end of a spectrum and need specific approaches in monitoring and treatment of disease. After diagnosis, primarily established by imaging modalities, renal management should be focused on monitoring blood pressure and treating hypertension. Nephrological follow-up should be focused on renal function and renal volume. Renal transplantation may be considered in end-stage renal disease. In contrast, monitoring the hepatic phenotype should focus on therapeutic interventions in case of gastrointestinal symptoms regardless of cyst extent, as liver function stays intact.

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