

Chapter 17

The Liver and Polycystic Kidney Disease

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Abstract

The hereditary forms of polycystic kidney disease (PKD) include a wide range of heterogeneous diseases of great clinical importance, of which autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD) are the main forms. ADPKD is a multifactorial disorder characterized by bilateral renal cysts and usually affects adult patients. Liver cysts are the most common extrarenal manifestations of ADPKD and are often incidental findings and clinically insignificant. In contrast, ARPKD is a severe, typically early-onset form of renal cystic disease. ARPKD patients may present with

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clinically-significant congenital hepatic fibrosis, with portal hypertension, requiring close monitoring, surgical shunting procedures, and kidney and/or liver transplantation. ARPKD is also related to Caroli's disease, a rare autosomal recessive congenital syndrome characterized by multiple saccular dilatations of intrahepatic bile ducts, with predisposition to gallstones, cholangitis and renal cysts. Simple hepatic cysts can also arise from excessive proliferation and dilatation of the bile ducts and peribiliary glands, which are rare in children but their frequency increases with age. The cystic liver epithelial cells have specific receptors, cytokines and growth factors that stimulate and promote cell proliferation and cyst formation. In general, hepatocellular function remains relatively preserved in this group of liver diseases, but may result in complications due to mass effects. The pathogenic sequence and genetic profile of PKD-associated liver cyst formation and progression is under extensive investigation. Therapeutic strategies to prevent and retard renal and liver cyst growth should be available in the near future.

Keywords: ADPLD; Caroli's disease; Hepatic cystic dilatations; Hepatorenal fibrocystic disease; Polycystic liver disease

Introduction

Adult liver cystic lesions are classified as hereditary or developmental, neoplastic, inflammatory, or mixed lesions. The hereditary forms of polycystic liver disease (PLD) are associated with autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), or occur as a distinct genetic disease in the absence of renal cysts (1-3).

ADPKD is a multifactorial disorder characterized by the formation and growth of multiple fluid-filled renal cysts that progress over decades with attendant inflammation and fibrosis. The major extrarenal manifestation of ADPKD is PLD, which does not affect liver function, but represents a heterogeneous set of structural changes of the biliary tree development and causes symptoms related to mass effects when significant liver enlargement occurs (3-5). During fetal development, defects in genetic mechanisms and signaling pathways cause disruption in the biliary tree, leading to formation of cystic structures, which typically remain asymptomatic until adulthood, when they start growing under hormonal action and may become symptomatic (6). Often these cysts are incidental findings, and clinically insignificant. They are rare in children but their frequency increases with age in women, especially under hormonal influences such as pregnancies or estrogen replacement therapies (7). The hepatic cyst epithelial cells have estrogen receptors, growth factor similar to insulin-like growth factor-1 (IGF-1), other growth hormones and cytokines that when stimulated promote proliferation and cystic growth (8,9).

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In contrast, ARPKD is considered the severe form of renal cystic disease, frequently with multisystemic manifestations, including congenital hepatic fibrosis and portal hypertension, and requiring close monitoring, surgical shunting procedures, and kidney or liver transplantation (10). In addition, ARPKD can also be related to Caroli's disease, a rare autosomal recessive congenital syndrome characterized by multiple saccular dilatations of the intrahepatic bile ducts with predisposition to gallstones, cholangitis and renal cysts (11).

In PKD-associated PLD, specific mutations are identified in biliary epithelial cells that produce increased differentiation, proliferation and secretion, which results in the formation of cysts. However, in isolated PLD, hepatic cysts arise from excessive proliferation and dilatation of the bile ducts and peribiliary glands. Without an association with PKD, PLD produces larger cysts but has fewer complications when compared to the form associated with PKD, termed Autosomal Dominant Polycystic Kidney and Liver Disease. The frequency of PLD increases with age and may be underestimated by tomography and ultrasonography (12-15). In this chapter we will discuss PLD as part of ADPKD, ARPKD and as a distinct genetic disease in the absence of renal cysts.

Autosomal dominant polycystic kidney disease

ADPKD is one of the most common monogenic diseases characterized by the progressive development of renal and extrarenal cysts, with important variability in clinical expression (12,14,15). It has worldwide prevalence and affects 0.2% of the general population, or every 400 to 1,000 births (15), while isolated PLD is less prevalent than 0.01% (7). ADPKD is genetically heterogeneous with two identified genes: PKD1, which is located on chromosome 16p; and PKD2, on chromosome 4q21. These genes encode proteins called polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Mutations of PKD1 represent 86% of cases, while mutations of PKD2 represent the rest of 14% (13,16,17), which trigger the formation of renal and hepatic cysts (Table 1). Despite genetic mutation, other factors are also involved in cystogenesis, such as age, female sex, pregnancy and oral contraceptive use (9).

PLD, as the most common extrarenal manifestations of ADPKD (12,15), is characterized by multiple biliary cystic lesions localized in over 50% of the hepatic parenchyma. Cystic size can range from 20 to 30 cm to small microscopic nodules. Patients with ADPKD have associated PLD in 75% -90% of cases (17,18). In ADPKD, hepatic cysts develop later than the renal cysts. The hepatic cysts are often incidental findings and clinically insignificant, often presented for the first time in the fourth decade of life and continuing to grow gradually with age in number and size. They are infrequent before age 20, with an

estimated prevalence of 20% in the third decade to 70% in the seventh decade of life (19,20). Both sexes are affected; however, women have a higher prevalence. Exposure to estrogen during pregnancy, use of oral contraceptive pills or estrogen replacement therapy seems to accelerate its progression (7,20). In women, under hormonal influence, the cysts can grow quickly, and when they reach high volume, the cysts can cause liver parenchyma atrophy (21).

In ADPKD with extrarenal manifestations of PLD, the liver cysts arise from the expansion of the bile microhamartomas and peribiliary glands, resulting from bile ducts epithelium overgrowth in the intralobular portion (14,17,22,23).

Autosomal recessive polycystic kidney disease

ARPKD is rare and typically of childhood onset. It occurs in 1: 6.000 to 1: 50,000 live births (29-32). ARPKD is caused by mutations in a single gene, polycystic kidney and hepatic disease 1 (PKHD1) gene, encoding a protein called fibrocystin/polyductin (29,30-34). Once the mutations of fibrocystin/polyductin occur, the structure of tubular epithelial cells lead to polarity disorders and emergence of cysts (33). In ARPKD, there is a genotype-phenotype correlation, in that the presence of two completely inactivating PKHD1 mutations results in a more severe clinical outcome associated with perinatal mortality (29,30-32). Patients with at least one hypomorphic missense mutation have a more juvenile presentation, suggesting that a subset of missense changes result in reduced rather than absent function of the PKHD1 gene product (30,31,35). Fibrocystin localizes in the cortical and medullary collecting ducts and thick ascending limbs of the loop of Henle in the kidney, but is also expressed in the bilio-pancreatic tracts, and in salivary ductal epithelia (33). Fibrocystin regulates planar cell polarity, and the complete loss of this protein leads to loss of oriented cell division (34).

Table 1. Comparison between polycystic kidney disease associated with hepatic cysts and isolated hepatic polycystic disease (12-28)

Clinical form	Polycystic kidney disease associated with hepatic cysts	Isolated hepatic polycystic disease
Prevalence	0-20%	<0.01%
Type of inheritance	Autosomal Dominant	Autosomal Dominant
Mutated genes	PKD1; PKD2	Prkcsh; Sec63
Encoded proteins	Polycystin 1; Polycystin 2	Hepato Cystin; Sec 63 protein
Chromosomal locus	16p; 4q21	19p; 6q21

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ARPKD is characterized by non-obstructive fusiform dilatation of the renal collecting ducts and malformations of the biliary tract, with ectasia of the bile ducts and periportal fibrosis (29). It can manifest in neonates with exaggerated kidney growth, intrauterine renal failure and pulmonary hypoplasia, or may present later with renal failure accompanied by portal and systemic hypertension (30). ARPKD is associated with a high level of morbidity and mortality in affected individuals who require close monitoring, surgical shunting procedures, and kidney and/or liver transplantation (29,32).

ARPKD is also related to the Caroli's disease, which is a rare congenital syndrome with the same pattern of inheritance (autosomal recessive) characterized by multiple saccular dilatations of the intrahepatic bile ducts, and with a predisposition to the formation of gallstones, to cholangitis and cystic kidney (11). It is common in childhood and the second decade of life and may be associated not only with different degrees of renal cysts, but also renal tubular ectasia, nephrocalcinosis, and interstitial fibrosis and renal failure (29-31).

Autosomal dominant polycystic liver disease

PLD is an inherited condition characterized by the presence of multiple scattered cysts of biliary origin throughout the liver parenchyma. PLD occurs not only as an extra-renal manifestation of ADPKD (MIM173900 and MIM173910), but also in patients with autosomal dominant PLD (ADPLD; MIM174050), an entity that is genetically distinct from ADPKD and not typically associated with renal cysts (30,35).

PLD is classified according to the number, size and the amount of remaining liver parenchyma (7):

- Type I - unlimited number of large cysts (greater than 10 cm);
- Type II - diffuse involvement of the hepatic parenchyma by multiple medium sized cysts with large remaining areas of hepatic parenchyma without cysts;
- Type III - diffuse and massive involvement of the hepatic parenchyma by small and medium cysts and only a few areas of normal liver parenchyma between the cysts, the most severe form of the disease.

The genes involved in ADPLD are *PrkcsH* and *Sec63* and encode hepatocystin and Sec63p, respectively (Table 1). Unlike other cystoproteins, hepatocystin and Sec63p are not ciliary proteins; they are components of the molecular machinery involved in the translocation, folding and quality control of newly synthesized glycoproteins in the endoplasmic reticulum (35-40). Most mutations are truncating and probably conduct to a complete loss

of the corresponding proteins and a defective processing of key regulators of biliary cell growth. The finding that PLD is caused by proteins involved in oligosaccharide processing was unexpected and implicates a new avenue for research into neocystogenesis, and might ultimately result in the identification of novel therapeutic drugs (39-41).

The gene products of *PrkcsH* and *Esa63*, glucosidase II β and *Sec63p*, are located in the endoplasmic reticulum and they are responsible for quality control machinery through which 30% of proteins encoded by the human genome pass, yet heterozygous mutations in these genes manifest only with bile duct cysts indistinguishable from the liver phenotype in ADPKD. Mutations in the *PrkcsH* and the *Sec63* genes solely determine hepatic cyst formation (40-42).

Pathogenesis of hepatic cysts

In the human embryo, the first sign of the bile ducts and the liver is the hepatic diverticulum, also known as the liver bud. For up to 8 weeks of gestation, the extrahepatic biliary tree develops through lengthening of the caudal part of the hepatic diverticulum. This structure is patent from the beginning and as it is, remains in continuity with the developing liver at all stages. The hepatic duct (*ductus hepaticus*) develops from the cranial part (*pars hepatica*) of the hepatic diverticulum. The distal portions of the right and left hepatic ducts develop from the extrahepatic ducts and are clearly defined tubular structures by 12 weeks of gestation. The proximal portions of the main hilar ducts derive from the first intrahepatic ductal plates. The extrahepatic bile ducts and the developing intrahepatic biliary tree maintain luminal continuity from the very start of organogenesis throughout further development. The normal development of intrahepatic bile ducts requires finely timed and precisely tuned epithelial-mesenchymal interactions, which proceed from the hilum of the liver toward its periphery along the branches of the developing portal vein. Lack of remodeling of the ductal plate results in the persistence of an excess of embryonic bile duct structures remaining in their primitive ductal plate configuration. This abnormality has been termed the ductal plate malformation (36-39).

Hepatoblast differentiation into a tubular biliary phenotype is stimulated by growth factors and signaling pathways, such as Notch, transforming growth factor- β (TGF- β) and Wnt. This transformation and cellular remodeling are completed after the 30th week of pregnancy. Intrahepatic ducts and extrahepatic ducts then merge and share the hepatic hilum. During the first year of life, the biliary system continues its development (37,38). Processes involved in hepatic cystogenesis include ductal plate malformation with concomitant

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abnormal fluid secretion, altered cell-matrix interaction and cholangiocyte hyperproliferation. The ductal plate malformation is a developmental portobiliary system abnormality and the basis of the biliary liver disease that manifests with congenital hepatic fibrosis, Caroli's syndrome, and PLD (28,45-46). In spite of that, hepatocellular function remains relatively preserved in this group of liver diseases associated to ductal plate malformation (28).

Based on experimental models of bile dysmorphogenesis, a new classification for the defects of the ductal plate was recently proposed: 1) dedifferentiation of abnormal hepatoblasts; 2) failure in bile duct maturation; and 3) ductal expansion disturbance, (18). Bile duct formation requires a network of epithelial and mesenchymal interactions, the presence of growth factors and transcription to direct and guide the migration, adhesion and differentiation of cholangiocytes (4,36,37).

The genetic connection between ADPKD and ADPLD

ADPLD is associated with mutations in the PKD1 and PKD2 genes. Carriers of mutations in the PKD1 gene have more renal complications compared to patients with PKD2 mutations (16-18,30). Recently, it has been shown that glucosidase II α and Sec63p are required in mice for adequate expression of a functional complex of the polycystic kidney disease gene products, PC1 and PC2. The authors found that PC1 is the rate-limiting component of this complex and that there is a dose-response relationship between cystic dilation and levels of functional PC1 following mutation of *PrkcsH* or *Sec63*. Reduced expression of PC1 also sensitizes the kidney to cyst formation resulting from mutations in *Pkhd1*. Proteasome inhibition increases steady-state levels of PC1 in cells lacking glucosidase II β and reduces cyst growth in orthologous mouse models of human ADPLD (40,41,43).

In addition, Cnossen *et al.* (44) identified that the low density Lipoprotein Receptor-related Protein 5 (LRP5) gene is the third locus associated with isolated PLD. It has been postulated that LRP5 variants may render ADPKD patients more susceptible to the development of polycystic liver. Cnossen *et al.* (44) have demonstrated that this gene may also have a role in unlinked and sporadic ADPKD patients. The authors have identified a total of four different LRP5 variants that were predicted to be pathogenic by *in silico* tools. One ADPKD patient has a positive family history for ADPKD and variant LRP5 c.1680G>T; p.(Trp560Cys) segregated with the disease. Although two PKD1 variants probably affecting protein function were also identified, luciferase activity assays presented for three LRP5 variants significantly decreased signal activation of canonical Wnt signaling. This

study contributes to the genetic spectrum of ADPKD, especially by the study of canonical Wnt signaling pathway that provides new insights for its pathophysiology (44). Experimental models have shown that other genes may also be associated with renal cystogenesis, for example, HNF1 β mutations may affect the progression and outcome of the renal cyst formation as well as ADPLD (41).

Clinical symptoms

Typically, PLD is asymptomatic, but the symptoms become more frequent with age, and so increase as a result of increased life expectancy, especially in patients with ADPKD due to dialysis and transplantation. Hepatic cysts are more prevalent and hepatic cyst volume is larger in women than in men, and multiple bile cystic lesions vary from 20 to 30 cm to small microscopic nodules (41,42). The clinical course of PLD is relatively benign compared with ADPKD. The symptoms may result from mass effects or complications related to the cysts. The symptoms that are typically caused by mass effects are hepatomegaly and portal hypertension, ascites, jaundice, hemorrhage, dyspnea, early satiety and weight loss, gastro-oesophageal reflux and pain in the lower back region (42-45). Symptomatic cyst complications include cyst hemorrhage, infection, and rarely torsion, or rupture (46). Other complications of mass effect are vena cava compression and lower portal vein and bile duct compression that presents itself as obstructive jaundice (12,41,47,48).

Management

PLD patients had significantly lower quality of life compared to general population. The primary outcome measurement of PLD management is to reduce liver volume and relieve associated symptoms. Higher liver volumes were associated with a lower quality of life. Abdominal pain and dyspnea had a significant impact on this physical dimension. Supportive management with analgesics is the first-line treatment in patients with acute or chronic abdominal pain and tenderness (15,49-54).

The primary aim of PLD therapy is to reduce symptoms by curtailing hepatic cyst development. The treatment of choice is driven by individual complaints. Therapeutic interventions are not warranted in asymptomatic patients. Conservative treatment is recommended for most patients with PLD. For symptomatic patients, therapy should be directed to the prevalent symptoms. Recent advances in ADPKD pathophysiology have stimulated research for new therapeutic strategies. The primary aim is to interrupt cyst growth to allow abdominal decompression and ameliorate related symptoms. The target of

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such drugs are abnormal cellular signaling cascades, that lead to deregulated proliferation, cell dedifferentiation, apoptosis and fluid secretion (1, 7,15, 17, 53-58).

Because of the proliferative effect of estrogen on hepatic cysts, oral contraceptives containing estrogen and menopausal estrogen therapy should be administered at the lowest effective dose, or avoided in patients with ADPKD. The first advice to females with PLD and ADPKD with a history of multiple pregnancies and prolonged exogenous estrogen exposure is to stop oral contraceptives. Although not formally investigated, the use other (non-systemic) contraceptives such as an intra-uterine device may be an acceptable alternative (53).

In recent years, several randomized clinical trials have been performed to study quality of life and the effects of diverse drugs on the growth of renal and hepatic cysts (54-59). Drugs that have been tested in randomized clinical trials include the mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus (60), somatostatin analogues such as octreotide, lanreotide, pasireotide (61,62), and most recently, the vasopressin V2 receptor antagonist, tolvaptan (63). Additional drugs are being tested, which include among others, the Src-ABL tyrosine kinase inhibitor, bosutinib, triptolide, histone deacetylase (HdaC6), Cdc25A phosphatase, miRNAs and metalloproteinases that attenuate growth of hepatic cysts (64). Many of these targets have been evaluated in pre-clinical trials, suggesting their value as potential new therapies. Additional therapeutic strategies to retard cyst growth aim at blood pressure control via inhibition of the renin-angiotensin aldosterone system and the sympathetic nervous system. Invasive procedures are required in a selective patient group with advanced PLD, ADPKD or liver failure (59,63,65). The different invasive approaches with possible beneficial outcomes include cyst aspiration and sclerosis, open or laparoscopic fenestration, liver resection with fenestration, and liver transplantation (1,7,15,17, 21,56,66,67-71).

Conclusions

PLD can either co-exist with ADPKD and ARPKD or occur alone as ADPLD. ADPKD and ARPKD as well as ADPLD are a group of genetic disorders initiated by mutations in several related genes, which results in the changes in cell signaling pathways to regulate cyst initiation and progression. The gene products of ADPLD may be required in mice for adequate expression of a functional complex of the ADPKD gene products, PC1 and PC2. The progression of the disease occurs throughout the patient's life with possible deterioration of renal and liver function. The main risk factors for growth of liver cysts are female sex, exogenous oestrogen use and multiple pregnancies. Individuals diagnosed

with isolated PLD or PKD associated PLD should be monitored for signs and symptoms. The main diagnostic methods of hepatic involvement are ultrasound, tomography, magnetic resonance imaging, and laparoscopy as an alternative. In selected cases, study of genetic mutations may be required.

PLD is usually benign, but can cause debilitating abdominal symptoms in some patients. In spite of that, hepatocellular function remains relatively normal, but major morbidity associated with hepatic fibrosis is portal hypertension, often leading to esophageal varices and hypersplenism. Although PLD is not typically associated with portal hypertension, but it may result in complications due to mass effects (vena cava compression, obstructive jaundice). Current radiological and surgical therapies for symptomatic patients include aspiration-sclerotherapy, fenestration, segmental hepatic resection and liver transplantation. Medical therapies that interact with regulatory mechanisms controlling expansion and growth of liver cysts are under investigation.

Conflict of Interest

The authors declare that they have no conflict of interest with respect to research, authorship and/or publication of this book chapter.

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