Autosomal Recessive Polycystic Kidney Disease—The Clinical Aspects and Diagnostic Challenges

Dorota Wicher[1] Łukasz Obrycki[2] Irena Jankowska[3]

[1] Department of Medical Genetics, Children's Memorial Health Institute, Warsaw, Poland
[2] Department of Nephrology, Kidney Transplantation and Hypertension, Children's Memorial Health Institute, Warsaw, Poland
[3] Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, Children's Memorial Health Institute, Warsaw, Poland

Address for correspondence Dorota Wicher, MD, Department of Medical Genetics, Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland (e-mail: d.wicher@ipczd.pl).

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Abstract

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most common ciliopathies with kidney (nephromegaly, hypertension, renal dysfunction) and liver involvement (congenital hepatic fibrosis, dilated bile ducts). Clinical features also include growth failure and neurocognitive impairment. Plurality of clinical aspects requires multidisciplinary approach to treatment and care of patients. Until recently, diagnosis was based on clinical criteria. Results of genetic testing show the molecular basis of polycystic kidneys disease is heterogeneous, and differential diagnosis is essential. The aim of the article is to discuss the role of genetic testing and its difficulties in diagnostics of ARPKD in children.

Keywords

- autosomal recessive polycystic kidney disease
- congenital hepatic fibrosis
- next-generation sequencing

Introduction

The aim of the article is to discuss the role of genetic testing and its difficulties in diagnostics of autosomal recessive polycystic kidney disease (ARPKD) in children.

We have done systematic searching of databases: PubMed, OVID, and Elsevier database with the following keywords: autosomal recessive polycystic kidney disease, congenital hepatic fibrosis, ciliopathies, phenocopies, genetics, molecular testing, next-generation sequencing, and prenatal diagnosis. We analyzed the literature on ARPKD and respective section in GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1326/ and referred to available expert consensuses and recommendations.

ARPKD (ARPKD, OMIM#263200), one of the most common ciliopathies with kidney and liver involvement, is an important cause of chronic kidney disease (CKD) in children.

Ciliopathies comprise a group of disorders resulting from abnormal formation or function of cilia. In general, cilia are classified as motile or nonmotile (primary). Numerous motile cilia are present on the surface of epithelial cells lining the airways, brain ventricles, and oviducts, while single primary cilia are present on most cells in the human body. The primary cilium coordinates a series of signal transduction pathways (including Hedgehog, Wnt, and platelet-derived growth factor receptor α) as well as works as a photo-, mechano-, and osmoreceptors. Ciliary dysfunction can manifest as a constellation of features that include retinal degeneration, renal disease, cystic pancreatic and liver diseases, cerebral anomalies, anosmia, polydactyly, and other developmental defects.[1–3]

Autosomal dominant polycystic kidney disease (ADPKD) and ARPKD are the most common ciliopathies associated with both liver and kidney diseases, but variable degrees of renal and/or hepatic involvement are seen in many other ciliopathies, including Joubert's, Bardet–Biedl's, Meckel–Gruber's, and oral–facial–digital syndromes.[4]

The phenotype of ARPKD is highly variable with a broad spectrum of symptoms and signs. In the majority of patients, it manifests as a severe form with onset in the prenatal/neonatal period.

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Etiology and Prevalence

ARPKD, whose incidence is estimated at 1/20,000 live births (carrier frequency 1:70 in nonisolated populations) is associated with pathogenic variants in the *PKHD1* gene (*Polycystic Kidney and Hepatic Disease 1* gene) located on chromosome 6p12.3-p12.2. *PKHD1* is one of the largest known human genes (more than 469 kb, 86 exons) and encodes a large transmembrane protein known as fibrocystin or polyductin. *PKHD1* is predominantly expressed in kidneys, with a much lower transcript expression detected in the pancreas and liver (bile ducts). The exact function of fibrocystin remains unclear. This protein might be involved in cellular adhesion, repulsion, and proliferation. Its location in the basal body of the apical domain building primary cilia of polarized epithelial cell suggests that fibrocystin may act as a receptor in signaling pathways crucial for organ morphogenesis.[5–7]

A recent study indicates that *DZIP1L* gene might also be involved in ARPKD pathogenesis.[8,9] Moreover, mutations in several other genes can produce a phenocopy of ARPKD (see Differential Diagnosis).[10,11]

Clinical Course

There are various clinical courses of ARPKD, ranging from a severe form with the onset during pregnancy to a clinically silent disease with no overt manifestation until adulthood. In late-onset cases, liver-related symptoms may dominate.

In patients with a history of oligohydramnios, dysmorphic features such as micrognathia, low-set ears, depressed nasal bridge, and limb positioning defects may be present.

Prenatal Phenotype

Prenatal ultrasonography may reveal enlarged, hyperechogenic kidneys, oligohydramnios, or an empty urinary bladder. Normal sonographic findings during pregnancy do not exclude the diagnosis of ARPKD as abnormalities may not be visible until the end of the second trimester or beyond.[12] Although signs of liver involvement usually are not detectable during pregnancy, there are a few reports in the literature on prenatally diagnosed Caroli's syndrome.[13]

Severely affected fetuses display a "Potter-like" oligohydramnios phenotype with lethal pulmonary hypoplasia, massively enlarged kidneys, characteristic facies, and contracted limbs with clubfoot.

The mortality rate in the early- and severe-onset forms of ARPKD is still high. The analysis of 52 children with ARPKD published by Roy et al revealed that 23% of patients died in the first year of their life (7 infants due to respiratory failure, and another 5 as a result of end-stage renal disease [ESRD]).[14]

Kidney Manifestations

The majority of ARPKD cases are identified late in pregnancy or at birth.[15] Prenatal diagnosis is possible during the second- or third-trimester ultrasound (US) scan, although in rare cases, it can be suspected as early as 15 weeks of gestation.[16] The main prenatal ARPKD US findings include very large (>4 standard deviation), diffusely hyperechoic kidneys without corticomedullary differentiation with or without evident cysts (classical cysts tend to develop after birth) and oligohydramnios.[17] Another less frequent but more characteristic pattern of enlarged hyperechoic kidneys with inversion of the corticomedullary differentiation was also described in ARPKD fetuses.[16,17]

After birth, these children may have enlarged kidneys that can appear to occupy the entire abdominal cavity on palpation. This makes it difficult to identify splenomegaly, which can occur as early as the perinatal period. Oligohydramnios is found in 33% of all ARPKD cases and in 90% of prenatal diagnoses.[18]

The postnatal renal sonographic phenotype can be variable: kidney size may range from normal to massively enlarged, hyperechogenicity can be limited by the medulla or diffuse, and cysts can appear as ductal dilatation or as macrocysts of variable size, number, and location. However, the classic US appearance of ARPKD shows bilaterally enlarged kidneys with heterogeneous parenchymal echogenicity with a salt-and-pepper pattern (caused by multiple tiny barely detectable cysts, which disrupt the echo pattern without being clearly distinguishable).[19] The salt-and-pepper pattern is mainly visible in children older than 6 years.

Recently, Iorio et al reported that salt-and-pepper pattern may also be seen in other ciliopathies.[20]

Urine output is usually not diminished, although oliguria may occur in some neonates. Hyponatremia and overt acute renal failure are also seen in the neonatal period.

Hypertension, often severe and difficult to control, affects a high percentage of ARPKD patients (up to 75–80%). Hypertension, specifically with hyponatremia may present in the neonatal period. Later, the tendency to hyponatremia gradually decreases and arterial hypertension is renin dependent, and it is only as the disease progresses and glomerular filtration decreases that salt and water retention begins to dominate. Despite these observations, the pathogenesis of systemic hypertension in ARPKD is not completely understood, and a link between hyponatremia, intravascular volume expansion, and low renin level is not proven.[21] Results of the research conducted by Goto et al showed that intrarenal, but not systemic, renin–angiotensin system activation is a prominent feature of ARPKD. Intrarenal renin and angiotensin-converting enzyme (ACE) gene upregulation may represent a novel mechanism for hypertension development or exacerbation in ARPKD.[22]

Changes in anatomical conditions in patients with ARPKD due to enlarged kidneys may predispose to urinary tract infections that can occur in up to 52% of children with ARPKD.[23]

In some patients with ARPKD (especially in premature infants), pyramidal hyperechogenicity can mimic an ultrasonographic pattern seen in medullary nephrocalcinosis.[24]

In newborns with an established diagnosis of ARPKD, who did not require renal replacement therapy (RRT), there is a gradual increase of renal size. Glomerular filtration values may improve in the first year of life, which is associated with the maturation of renal function.[25]

In further observation, ARPKD results in progressive decrease of renal function to ESRD in ~50% of patients, usually in the first decade of life.

The risk factors for early dialysis dependency include oligohydramnios/anhydramnios, kidney enlargement, renal cysts on prenatal US, as well as low Apgar scores and the need for assisted breathing or ventilation.[18]

Liver Manifestations

Liver involvement is invariably present in all ARPKD patients and hepatobiliary complications may dominate in older patients.

Biliary dysgenesis (ductal plate malformation with associated periportal fibrosis) results in congenital hepatic fibrosis (CHF) and/or dilatation of intrahepatic bile ducts.[26]

While histological abnormalities are present from early embryonic period, clinical and radiological signs of liver involvement are time dependent and manifest later in life.

Liver enzyme levels are typically within normal ranges, but markers of cholestasis (e.g., gamma-glutamyl transferase, alkaline phosphatase) may be elevated (especially in teens or young adults).

Liver fibrosis is progressive and leads to development of portal hypertension and its consequences (hypersplenism, splenomegaly, esophageal varices, gastrointestinal bleeding, ascites) in the majority of patients (up to 70%).

In addition to CHF, nonobstructive dilatation of the intrahepatic bile ducts (Caroli's syndrome) and dilatation of the common bile duct occur in more than 60% of individuals with ARPKD.[27] It is associated with an increased risk of ascending cholangitis. Adult ARPKD patients are at slightly increased risk of cholangiocarcinoma.[28]

Rare Findings in ARPKD

In contrast to ADPKD, vascular abnormalities are not typical for ARPKD.[29] Until now, a few ARPKD patients (clinical diagnosis not confirmed by molecular testing) with intracranial or extracranial aneurysms were reported.[30–32]

Pancreatic cysts in a few patients were also described.[21]

Other Clinical Aspects

Feeding difficulties are often seen in children with ARPKD. They may result from mechanical compression of the stomach by enlarged organs (kidneys, liver, spleen) as well as from loss of appetite and/or impaired gastric motility due to significant renal impairment.[27]

Indications and contraindications for gastrostomy in children with ARPKD were recently discussed by Burgmaier et al.[33]

Inadequate nutrition may lead to growth disturbance. Impaired growth is observed in a majority of ARPKD pediatric patients; however, their height is comparable to children with other causes of CKD. Apart from inadequate nutrition, the risk factors for growth impairment include prematurity, low birth weight, intensive care unit hospitalization, and early-onset CKD.[34]

ARPKD might be associated with neurological and neuropsychological impairments, due to exposure to various risk factors during critical periods of brain development. Prematurity, chronic hypertension (small vessel damage), liver disease (potential minimal hepatic encephalopathy), and chronic lung disease can contribute to neurocognitive deficit and dysfunction. Furthermore, ARPKD patients who require dialysis or kidney and/or liver transplantation may struggle with lower quality of life, disrupted family dynamic, low self-esteem/poor self-perceived attractiveness, and depressed mood.[35]

Diagnosis

ARPKD should be suspected in patients with bilateral hyperechogenic, enlarged kidneys with poor corticomedullary differentiation, with or without a history of oligohydramnios and cysts.

Diagnostic criteria of ARPKD are presented in ►**Table 1**. Clinical criteria may be difficult to fulfill in small families with one child and young parents. The diagnosis of ARPKD is unquestionable only in a proband with typical clinical findings and biallelic pathogenic variants in *PKHD1* gene.

Marked allelic heterogeneity characterizes the mutational spectrum in *PKHD1*, as different types of variants, missense, and truncating (nonsense, frameshift, splice site) are distributed along the whole gene. Most of them are missense (60–77%). Variants are often novel and unique to single families in "nonisolated" populations.[11,15,36–39]

In ARPKD, genotype–phenotype correlations depend on types of mutations. The most severely affected patients typically have two truncating mutations, while patients with milder phenotype have two missense or a missense and a truncating change.[15,39]

Genetic testing allows to detect molecular basis of ARPKD in $\sim$ 73% of patients by sequence analysis of *PKHD1* gene and in further 1 to 2% of patients by gene-targeted deletion/duplication analysis. Pathogenic variants in *DZIP1L* account for $<$ 1% of cases.[27]

An ARPKD-like phenotype (ARPKD phenocopies) may result due to pathogenic variants in other genes, which should be included during molecular testing. Currently, the most efficient

Table 1 Diagnostic criteria of ARPKD (modified from Zerres et al)[60]

Ultrasonographic findings typical of ARPKD
Increased renal size (in relation to normative size based on age and length/height of the affected individual)
Increased echogenicity
Poor corticomedullary differentiation
AND
One of more of the following
Absence of renal cysts by sonography in both parents, particularly if they are >40 years old
Clinical, laboratory, or radiographic evidence of hepatic fibrosis
Hepatic pathology demonstrating characteristic ductal plate abnormalities
Previous affected sibling with molecularly confirmed disease
Parental consanguinity suggestive of autosomal recessive inheritance

Abbreviation: ARPKD, autosomal recessive polycystic kidney disease.

diagnostic approach is the next-generation sequencing (NGS) (targeted NGS panels containing polycystic kidney disease [PKD]-related genes).

As mentioned earlier, copy number variations (CNVs) are not frequent in ARPKD. However, CNVs have a significant share in nephronophthisis (NPHP)1 variants (20–25%). Gene-targeted deletion/duplication analysis is required also to detect 17q12 microdeletion (*HNF1B* gene) and *TSC2-PKD1* microdeletion.

In summary, the testing approach for PKD should be able to detect single nucleotide polymorphisms as well as CNVs. Moreover, it is worth remembering that the presence of pseudogenes (e.g., six *PKD1* pseudogenes) can make analysis more sophisticated.

In families with an established molecular diagnosis, carrier testing (by Sanger sequencing or CNV-related methods) is possible.

Given that normal prenatal US examination does not exclude ARPKD, definitive prenatal diagnosis is often only reliably attainable through genetic screening.[15] Such procedure requires chorionic villus sampling or amniocentesis and is offered to families with known risk of ARPKD when the pathogenic variants in *PKHD1* have been identified in an affected family member. Preimplantation genetic diagnosis is another possible option in these families, providing the opportunity to avoid the physical and emotional trauma of a pregnancy termination in the case of an affected fetus.[40]

When the family history is negative, and suspicion of ARPKD is made first time during pregnancy, the prenatal diagnostics is more challenging. Fetal sequencing using targeted clinical panels or whole exome sequencing is possible, but there are many difficulties to overcome (e.g., time constraints, limited data on fetal phenotype, highly complex interpretation of results and posttest counseling, costs). The routine use of prenatal sequencing as a diagnostic test is not currently recommended due to insufficient data validation and uncertain balance of its benefits and pitfalls.[41]

Differential Diagnosis

There are diseases which may imitate ARPKD phenotype.

The most important entity in differential diagnosis of ARPKD is ADPKD (early disease manifestation).[15] Although most patients have an affected parent, a negative family history does not exclude ADPKD diagnosis (e.g., possible de novo pathogenic variant, early death of parent before the onset of symptoms).

Typically, the onset of ADPKD is in adulthood, however, 2 to 5% of affected individuals present in the prenatal/neonatal period, often with signs and symptoms indistinguishable from those of ARPKD.

CHF, an invariable finding in ARPKD, was reported as well in some ADPKD patients.

The leading cause of hyperechoic fetal kidneys is *HNF1β*-related disease. Kidneys are usually normal sized on prenatal US examination, but severe ARPKD-like phenotype may also occur. Extrarenal manifestations include endocrine/exocrine insufficiency (e.g., diabetes), genital malformations, hypomagnesemia, hyperuricemia, and elevated liver enzymes.

Early- and severe-onset PKDs may be observed also in NPHP, an autosomal recessive form of progressive tubulointerstitial disease, progressing to ESRD in childhood or in adolescence. About 10% of patients with NPHP have extrarenal manifestations.[42]

TSC2-PKD1 microdeletion should be taken into consideration in patients with early and severe onset of PKD and coexisting tuberous sclerosis symptoms.

Polycystic kidney disorders with possible prenatal onset are presented in ►**Table 2**.

When prenatally detected hyperechogenic enlarged kidneys coexist with other abnormalities, other ciliopathies (e.g., Meckel's syndrome, short-rib polydactyly syndromes, Bardet–Biedl's syndrome, Joubert's syndrome, Jeune asphyxiating dysplasia), as well as Beckwith–Wiedemann's syndrome should be considered in the differential diagnosis. Severe oligohydramnios and mildly increased kidney echogenicity can be a feature of renal tubular dysgenesis, while enlarged kidneys and placenta may point to congenital nephrotic syndrome type 1 (Finnish type). Renal cysts may be detected prenatally also in some metabolic disorders: Smith–Lemli–Opitz's syndrome, peroxisome biogenesis disorders, glutaric aciduria type 2, and neonatal form of carnitine palmitoyltransferase II deficiency.[43]

In 2017, pathogenic variants in the *PMM2* gene (phosphomannomutase 2) resulting in an ARPKD and hyperinsulinism were described in 11 families.[44]

The differential diagnosis of PKD in adolescent or adult patients should also take into account for *MUC1* and *UMOD*-related autosomal dominant tubulointerstitial kidney diseases.

Accurate analysis of family history and parental renal US should be done in every pediatric patient with PKD of unknown origin.

Management

Patients with ARPKD should be under the care of a multispecialist team consisting of a nephrologist, gastroenterologist, and dietitian.

After initial diagnosis of ARPKD, assessment of kidney and liver function is required. Recommended diagnostic scheme is presented in ►**Table 3**.

Treatment focuses on managing pulmonary hypoplasia, chronic renal disease, systemic hypertension, and liver-related complications. Mechanical ventilation may be necessary in patients with pulmonary hypoplasia or hypoventilation (massively enlarged kidneys prevent diaphragmatic excursion).

In children with hypoventilation and/or severe feeding intolerance, unilateral or bilateral nephrectomy (with placement of a peritoneal dialysis [PD] catheter) should be taken into consideration.[45,46]

Factors affecting the timing of this surgical intervention include age, size, and clinical status of the patients and availability of a potential kidney donor.

Symptomatic treatment is typical for CKD. The complication characteristics of ARPKD include hypertension with hyponatremia in newborns and infants associated with water

Table 2 Polycystic kidney disorders with possible prenatal onset

	ARPKD	ADPKD	*HNF1B*-related disease	NPHP	*TSC2-PKD1* microdeletion
Prevalence	1:20,000	1:500–1:1,000	Not known	1:50,000–1:1,000,000	Not known
Gene(s)	*PKHD1*	*PKD1*, *PKD2* *GANAB*, *DNAJB11*	*HNF1B*, deletion 17q12	*NPHP1*, *INVS*, *NPHP3*, *NPHP4*, *IQCB1*, *CEP290*, *GLIS2*, *NEK8*, *TMEM67*, *TTC21B*[a], *WDR19*, *ZNF423*[a], *CEP164*, *ANKS6*, *CEP83*, *DCDC2*, *MAPKBP1*	*TSC2*, *PKD1*
Inheritance	AR	AD	AD	AR, AD[a]	AD
Typical renal ultrasonography findings[19]	Bilaterally enlarged kidneys with heterogeneous parenchymal echogenicity with a salt-and-pepper pattern[b] Other forms of the renal sonographic phenotype are possible: kidney size may range from normal to massively enlarged, hyperechogenicity can be limited by the medulla or diffuse, and cysts can appear as ductal dilatation or as macrocysts of variable size, number, and localization *Prenatal US*: large hyperechogenic kidneys and oligohydramnios in severe cases	Multiple cortical and medullary cysts. Number of cysts increase with age Possible prenatal presentation with subtle cortical hyperechogenicity and renal enlargement	Variable findings: uni- or bilateral cysts, hypo- or dysplasia, agenesis, or normal kidney imaging The most common cause of kidney hyperechogenicity at prenatal US and of kidney cysts in older children Can mimic ARPKD and other cystic nephropathies	Nonspecific Juvenile NPHP: usually normal-sized or small kidneys and bilaterally increased echogenicity. Cysts are not mandatory for diagnosis. Cysts at the corticomedullary junction are suggestive for NPHP *Infantile NPHP*: usually enlarged kidneys with cortical microcysts	Kidney phenotype with numerous bilateral large cysts (>2.5 cm) that appear early in life, replace the renal parenchyma, and lead to kidney enlargement
Systemic hypertension	Severe, drug resistant in the first months of life	Before 15 years of life in early manifestation of ADPKD	No data	Not clinically relevant until late stage of the disease	No data
Hepatic fibrosis	100%	Rare	No	As extrarenal manifestation	No
Liver enzymes	Within normal ranges with the exception of GGTP which might be elevated	No data	Elevated	No data	No data
Median age of ESRD onset	1–2 decade of life	58.1 y (*PKD1*) 79.9 y (*PKD2*)	No data	Significant cause of ESRD <25 y	No data
Extrarenal findings	Sporadically: intracranial or extracranial aneurysms, pancreatic cysts	Polycystic liver disease, pancreatic cysts, seminal vesicle cysts, arachnoid membrane cysts, intra-/extracranial aneurysms, abnormalities of the aorta and cardiac valves, colonic diverticulosis	Abnormalities of the genital tract (vaginal and uterine anomalies), pancreatic anomalies (atrophy, partial agenesis), endocrine/exocrine insufficiency, hypomagnesemia, increase liver enzymes	A broad spectrum of celiopathy-related extrarenal signs may occur (10–20% of patients)	Signs of tuberous sclerosis (e.g., cardiac rhabdomyoma in fetus, hypomelanotic macules, subependymal nodules)

Abbreviations: AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; ARPKD, autosomal recessive polycystic kidney disease; NPHP, nephronophthisis; PKD, polycystic kidney disease; US, ultrasound.
[a]Nephronophthisis-related genes with possible autosomal dominant inheritance.
[b]Salt-and-pepper pattern is typical for ARPKD but may also be seen in other ciliopathies.[20]

retention and eating disorders caused not only by metabolic disorders in CKD but also by abdominal tightness syndrome caused by nephro- and hepatomegaly.

Hypertension with hyponatremia in ARPKD, generally observed in newborns with ARPKD, is associated with water retention, and the treatment involves the administration of furosemide and/or vaptans (vaptans are still not officially approved for use in children) and the introduction of fluid restriction and negative fluid balance.[47,48]

The treatment of choice in hypertension without hyponatremia is ACE inhibitors or angiotensin II receptor blockers. Due to portal hypertension, nonselective β-blockers (propranolol) can also be added.[21,47]

RRT, in the form of dialysis or transplantation, is indicated when patients progress to ESRD. PD is the preferred modality, particularly in young children. PD is indispensable in newborns with oliguria/anuria, after bilateral nephrectomy and when kidney involvement progresses to ESRD.

Table 3 Recommended evaluations following ARPKD diagnosis

Physical examination	**Respiratory status**	
	Abdominal examination (hepatomegaly, splenomegaly, nephromegaly)	
Laboratory examination	kidneys	Serum concentrations of BUN, creatinine, and cystatin C
		Serum electrolyte concentrations
		Urinalysis (specific gravity, osmolality, proteinuria)
	Liver	Transaminases activity
		Serum bile acids concentration
		Serum albumin concentration
		Coagulation parameters studies
		Fat-soluble vitamin levels
		Complete blood counts (to detect hypersplenism)
Radiologic imaging	Chest radiographs (as indicated)	
	Renal ultrasonography (consider high-resolution technology when available)	
	Abdominal ultrasonography to assess liver involvement	
Clinical assessment of intravascular volume status for possible volume depletion or overload		
Measurement of blood pressure		
Assessment of feeding, weight gain, and linear growth with formal nutrition consultation as appropriate		
Consultation with a clinical geneticist and/or genetic counselor		

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; BUN, blood urea nitrogen.

Primary prevention of gastrointestinal tract bleeding in patients with portal hypertension should be based on endoscopic variceal ligation. The routine use of nonselective β-blockers is not recommended in pediatric patients.[49,50]

In children with severe hypersplenism and/or splenomegaly, splenectomy or splenic embolization may be beneficial.[51]

In cases of suspected bacterial cholangitis (persistent/recurrent fever, right upper-quadrant pain), patients should be evaluated and treated aggressively. Chronic antibiotic prophylaxis is recommended in patients at high risk, including those with a previous episode of ascending cholangitis.[27,52]

Indications for liver transplantation in ARPKD patients include recurrent, endoscopically incurable bleedings from esophageal varices, recurrent cholangitis, and liver decompensation or encephalopathy.[53]

ARPKD is a major indication (besides primary hyperoxaluria) for combined liver and kidney transplantation during childhood.[54] ARPKD patients are at risk of feeding difficulties. Gastrostomy insertion may facilitate adequate supply of fluids and calories, as well as medication administration. Growth hormone therapy should be offered to ARPKD patients with growth failure.[55]

Premature patients < 24 months with or without chronic lung disease may benefit from palivizumab administration. Inpatients with splenic dysfunction immunization against encapsulated bacteria (pneumococcus, meningococcus, and *Haemophilus influenzae* type B) are indicated.

Prognosis

Pulmonary hypoplasia due to oligohydramnios/anhydramnios is a major cause of morbidity and mortality in the newborn period. In addition, massively enlarged kidneys may lead to hypoventilation and respiratory distress.[27] Fortunately, long-term pulmonary function prognosis is good in survivors.[56]

Long-term follow-up shows that 86% of children younger than 5 years, 71% at 10 years of age, and 42% at 20 years of age have impaired but still retained kidney function. Patients who were diagnosed with ARPKD during the perinatal period required RRT at the age of 7.6 years and those who were diagnosed later at an average age of 26 years.[57]

Approximately 10% of patients may require liver transplantation in the course of ARPKD.[58]

Future Perspectives

In recent years, considerable progress has been made in understanding of polycystic kidneys diseases. Molecular studies revealed considerable heterogeneity of disorders with cystic phenotype. Modern techniques are utilized to analyze all potential causative genes. In the future, noninvasive prenatal testing will likely become more prominent as the technology develops.[15]

Knowledge of the precise function of the gene and its protein product is essential to invent targeted therapies. Although the pathophysiology of ARPKD is still unclear, there are promising data suggesting that a unique multikinase inhibitor called tesevatinib may be a safe and effective therapy for ARPKD in children.[59]

Conflict of Interest
None declared.

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