PKD in Children: The Basic Principles and Clinical Care

Lisa M. Guay-Woodford, MD
Hudson Professor of Pediatrics
Director, Center for Translational Science
Director, Clinical and Translational Science Institute-Children’s National
Children’s National Medical Center and George Washington University

PKD National Convention
June 24-26, 2016

Objectives

Overview

ADPKD: key issues
- Data from clinical studies
- Diagnosis - radiologic; genetic
- Clinical issues and management

ARPKD: key issues
- Data from clinical studies
- Diagnosis - radiologic; genetic
- Clinical issues and management
Normal Kidney

The kidneys are a pair of reddish-brown organs located on either side of the spine just below the diaphragm, behind the liver and stomach. They are bean-shaped and about the size of one’s fist.

The primary function of the kidneys is to remove waste from the body through the production of urine. They also help to regulate blood pressure, blood volume, and the chemical (electrolyte) composition of the blood.

How do kidneys help maintain health?

- Remove wastes (e.g., urea) and excess fluid from your body through the production of urine
- Continuously regulate the body’s fluids and chemical composition (sodium, potassium, phosphorus and calcium)
- Remove drugs and toxins from your body
- Produce and release hormones into your blood
  - erythropoietin - stimulates the bone marrow to make red blood cells
  - renin - regulates blood pressure
  - calcitriol (a form of Vitamin D) - helps the intestine to absorb calcium from the diet, and thereby maintain healthy bones
Kidney handling of salt and water

<table>
<thead>
<tr>
<th>Filtered</th>
<th>Excreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>1,500 grams</td>
</tr>
<tr>
<td>Water</td>
<td>200 quarts</td>
</tr>
</tbody>
</table>

© 2016 CTSI-CN | CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE AT CHILDREN’S NATIONAL | CTSICN.ORG

Normal Liver

The liver is one of the largest and most complex organs in the body. It weighs ~1 pound and is made up of a spongy mass of wedge-shaped lobes. The liver has many functions that are necessary for life:

- helps process carbohydrates, fats, and proteins absorbed from food in the intestines and turns them into materials that the body needs for life.
- secretes bile to help digest fats.
- makes the factors needed for clotting.
- stores vitamins.
- breaks down toxic substances in the blood.

© 2016 CTSI-CN | CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE AT CHILDREN’S NATIONAL | CTSICN.ORG
PKD: what goes wrong

Definitions

Autosomal dominant PKD (ADPKD)

Autosomal recessive PKD (ARPKD)
Objectives

Overview

ADPKD: key issues
- Data from clinical studies
  - Diagnosis - radiologic; genetic
  - Clinical issues and management

ARPKD: key issues
- Data from clinical studies
  - Diagnosis - radiologic; genetic
  - Clinical issues and management

Autosomal Dominant PKD

- Occurrence: 1:800-1,000
- Genetics
  - PKD1: ~85%
  - PKD2: ~15%
- Kidney disease
  - bi-modal presentation
  - 1-2% nephrons affected
  - normal ➔ very large kidneys
- Other organ involvement
  - biliary cysts, pancreatic cysts
  - vascular aneurysms, hernias
  - male infertility

### Disease expression in ADPKD patients

<table>
<thead>
<tr>
<th></th>
<th>Early onset</th>
<th>Childhood onset</th>
<th>Adult onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of dx</td>
<td>prenatal-1 yr</td>
<td>--</td>
<td>20-40 yrs</td>
</tr>
<tr>
<td>Unilateral disease</td>
<td>rare</td>
<td>up to 20%</td>
<td>rare</td>
</tr>
<tr>
<td>Hematuria</td>
<td>UN</td>
<td>10%</td>
<td>35-50%</td>
</tr>
<tr>
<td>Microalbuminuria/proteinuria</td>
<td>UN</td>
<td>30%; 23%</td>
<td>25%; 17%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80%</td>
<td>22%</td>
<td>60%</td>
</tr>
<tr>
<td>Nephrolithiases</td>
<td>rare</td>
<td>rare</td>
<td>20%</td>
</tr>
<tr>
<td>ESRD</td>
<td>25%</td>
<td>rare</td>
<td>50%</td>
</tr>
<tr>
<td>Biliary cysts (MRI)</td>
<td>rare</td>
<td>55%</td>
<td>83%</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>UN</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>Intracranial aneurysms</td>
<td>rare</td>
<td>rare</td>
<td>5-7%</td>
</tr>
<tr>
<td>Inguinal hernias</td>
<td>UN</td>
<td>10%</td>
<td>3%</td>
</tr>
</tbody>
</table>


### Comparison of PKD1 vs PKD2 disease

<table>
<thead>
<tr>
<th></th>
<th>PKD1</th>
<th>PKD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (sx presentation)</td>
<td>42.0 yrs</td>
<td>56.0 yrs</td>
</tr>
<tr>
<td>ESRD</td>
<td>54.3 yrs</td>
<td>74.0 yrs</td>
</tr>
<tr>
<td>Overall survival</td>
<td>53.0 yrs</td>
<td>69.1 yrs</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Macroscopic hematuria</td>
<td>1.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Renal tract calculi</td>
<td>1.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Objectives

Overview

ADPKD: key issues
• Data from clinical studies
  ➢ Diagnosis - radiologic; genetic
• Clinical issues and management

ARPKD: key issues
• Data from clinical studies
• Diagnosis - radiologic; genetic
• Clinical issues and management

US imaging: diagnostic criteria for ADPKD

Ravine criteria
(PKD1 families)
15-29 years:
> 2 cysts (unilateral or bilateral)
30-59 years:
> 2 cysts in each kidney
> 60 years:
> 4 cysts in each kidney

Pei modified criteria
(families of unknown genotype)
15-39 years:
> 3 cysts (unilateral or bilateral)
40-59 years:
> 2 cysts in each kidney
> 60 years:
> 4 cysts in each kidney

US imaging: ADPKD

Fetal
- Enlarged, hyperechoic kidneys after 17 wks GA
- Usually normal amniotic fluid levels
- Discrete renal cysts (11%)

Childhood (0-15 yrs)
- Enlarged kidneys, discrete cysts, normal echogenicity
- One cyst adequate to make the diagnosis in an at-risk individual
- Ultrasound less sensitive than genetic testing for PKD1 and PKD2

Young adult (15-30 yrs)
- Enlarged kidneys, discrete cysts, normal echogenicity
- Ultrasound less sensitive than genetic testing for PKD1 and PKD2
  - PKD1 95% sensitivity
  - PKD2 67% sensitivity

Adult (>30 yrs)
- 97-100% sensitive, at least 2 cysts in each kidney needed for diagnosis
- Kidney enlargement in 95% PKD1 patients

Diagnostic strategies: genetic testing

ADPKD: PKD1 and PKD2

Mutations identified in 180 (89.1%) probands:
- 153 (85.0%) PKD1 and 27 (15.0%) PKD2

ADPKD: Recommendations for genetic testing

- Genetic testing is useful when imaging results are not conclusive and/or when a definite diagnosis is required in a younger individual, such as a potential living-related kidney donor.

- Genetic testing can be helpful with new mutations in the absence of a family history.

- Prenatal and pre-implantation genetic testing (PGD) are not commonly considered for ADPKD.

Objectives

Overview

ADPKD: key issues
- Data from clinical studies
- Diagnosis - radiologic; genetic
  - Clinical issues and management

ARPKD: key issues
- Data from clinical studies
- Diagnosis - radiologic; genetic
- Clinical issues and management
ADPKD treatment issues: Children

Kidney
- Hypertension
- Gross hematuria (visible blood in urine)
- Urinary tract infection
- Stones
- Dialysis and transplantation

Other
- Pain syndromes
- Symptomatic cystic liver disease
- Intracranial aneurysms
- Male infertility

Mechanisms of hypertension in ADPKD

Normal kidney

ADPKD kidney
Mechanisms of hypertension in ADPKD

- Renal cysts
- Renin
- Aldosterone
- Salt and Water retention
- Angiotensin II
- Vascular resistance
- Cell growth
- Hypertension

Objectives

Overview
ADPKD: key issues
- Data from clinical studies
- Diagnosis - radiologic; genetic
- Clinical issues and management

ARPKD: key issues
- Data from clinical studies
- Diagnosis - radiologic; genetic
- Clinical issues and management
Autosomal Recessive PKD

- Incidence: 1:20,000
- Genetics
  - PKHD1
- Kidney disease
  - 1° collecting ducts
  - very large kidneys
- Other organs involved
  - biliary dysgenesis and fibrosis

### ARPKD: comparative data

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. Am. Database (N=166*)</th>
<th>Bergmann (2005) (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal dx</td>
<td>46%</td>
<td>23%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>26%</td>
<td>UN</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>CRI</td>
<td>42%</td>
<td>86%</td>
</tr>
<tr>
<td>ESRD</td>
<td>13%</td>
<td>29%</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>12%</td>
<td>--</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>15%</td>
<td>44%</td>
</tr>
<tr>
<td>1-yr survival</td>
<td>92%</td>
<td>85%</td>
</tr>
</tbody>
</table>

### ARPKD: clinical data by age of diagnosis

#### TABLE 3. Clinical Manifestations at Diagnosis (65 Patients)

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 Year (n = 22)</th>
<th>1-20 Years (n = 23)</th>
<th>&gt;20 Years (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARPKD</td>
<td>22</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Isolated congenital hepatic fibrosis</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Kidney enlargement</td>
<td>15</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Symptomatic kidney stone</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>5/11</td>
<td>5/11</td>
<td>5/13</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>9</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Hypersplenium</td>
<td>5</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Variceal bleeding</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Familial screening</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

ARPKD: patient survival


ARPKD: kidney survival


Objectives

Overview
ADPKD: key issues
• Data from clinical studies
• Diagnosis - radiologic; genetic
• Clinical issues and management

ARPKD: key issues
• Data from clinical studies
  ➢ Diagnosis - radiologic; genetic
• Clinical issues and management

Hepato-Renal Fibrocystic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene(s)</th>
<th>Renal disease</th>
<th>Hepatic disease</th>
<th>Systemic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARPKD</td>
<td>PKHD1</td>
<td>Collecting duct dilatation</td>
<td>CHF, Caroli disease</td>
<td>no</td>
</tr>
<tr>
<td>ADPKD</td>
<td>PKD1; PKD2</td>
<td>Cysts along entire nephron</td>
<td>Biliary cysts; CHF (rare)</td>
<td>yes - adults</td>
</tr>
<tr>
<td>Nephronophthisis (NPHP)</td>
<td>NPHP1-NPHP19</td>
<td>Cysts at the cortico-medullary junction</td>
<td>CHF</td>
<td>+/-</td>
</tr>
<tr>
<td>Joubert syndrome and related disorders</td>
<td>JBTS1-JBTS26</td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF, Caroli disease</td>
<td>yes</td>
</tr>
<tr>
<td>Bardet-Biedel syndrome (BBS)</td>
<td>BBS1-BBS23</td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF</td>
<td>yes</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome (MKS)</td>
<td>MKS1-MKS12</td>
<td>Cystic dysplasia</td>
<td>CHF</td>
<td>yes</td>
</tr>
<tr>
<td>Glomerulocystic disease</td>
<td>PKD1; HNF1B (TCF2); UMOD</td>
<td>Enlarged; normal or hypoplastic kidneys</td>
<td>CHF (with PKD1 mutations)</td>
<td>+/-</td>
</tr>
<tr>
<td>Renal-hepatic-pancreatic dysplasia (Ivemark II)</td>
<td>NPHP3, NEK8</td>
<td>Cystic dysplasia</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>yes</td>
</tr>
</tbody>
</table>
ARPKD Diagnosis: Imaging

Prenatal
- Standard second-trimester US imaging is usually sufficient to suggest the diagnosis of ARPKD, especially if findings include bilateral, large echogenic kidneys with poor corticomedullary differentiation.
- Macrocysts (>10 mm) in the fetal ARPKD kidney are unusual and suggest multicystic dysplasia, whereas bilateral cysts of 5-7 mm are reported in 29% of ARPKD cases.
- A systematic evaluation should be undertaken for extrarenal anomalies given that other fetal conditions are associated with renal hyperechogenicity.

Post-natal
- High-resolution US may improve diagnostic sensitivity, particularly in mild disease.
- Unlike in ADPKD, kidney size/volume do not correlate with renal function in ARPKD.

Genetics

ARPKD: PKHD1

465 kb gene; 86 exons, 67 exons in the longest open reading frame
Likely pathogenic: 51%; Missense: 45%

Selected cohorts - mutations identified in 81-87% probands
Bergmann et al. (2005) Hum Mutat 25: 225-231. 80%
Losekoot M et al. (2005) Hum Genet 118: 185-206. 87%
Genome-level analyses

Whole exome analysis using Next Generation Sequencing (NGS)
- all EXons of the genome: ~180,000 exons, 1-2% of entire genome

Targeted Next Generation Sequencing (NGS)
- DNA enrichment (capture-based) of relevant genes followed by parallel sequencing using NGS platforms
- Specific set of genes (multi-gene panels)

Advantages:
- Only a portion of genome needs to be sequenced
- Achieve higher sequence coverage
PKD Foundation
PKD in Children-Basics
June 24, 2016

ARPKD “genotype-phenotype” correlations

- Limited correlation between specific gene defects / mutations (genotypes) and clinical disease (phenotypes).
- Two chain-terminating mutations are more frequently associated with perinatal demise, whereas at least one amino acid substitution is more commonly associated with a non-lethal presentation.

Bergmann et al. (2005) Kidney Int 67:829-848

ARPKD intra-familial variability

- Significant variability in ARPKD-related morbidities observed in 11/20 sibships.
- Significant differences survival and disease severity demonstrated in 20/48 sibships.
  Bergmann et al. (2005) Kidney Int 67:829-848
- Within-family variability in survival and ARPKD-related morbidities. In one sibship, affected children homozygous for delEx1-37. Two sibs suffered perinatal demise while their 8 yo brother has CKD and severe congenital hepatic fibrosis.
**ARPKD: Recommendations for genetic testing**

- Gene-based testing is primarily used in the context of prenatal testing and pre-implantation genetic diagnosis.

- To date, there is limited evidence for correlations between specific disease manifestations and specific kinds of genetic defects (mutations).

- The usefulness of *PKHD1* testing has largely correlated with the strength of the clinical dx; but this is changing with new genetic tools.

**Pre-implantation testing or genetic diagnosis (PGD)**

- Gigarel et al. (2008) Reprod Biomed Online. 16:152-158

* The isolated DNA is amplified by PCR to generate multiple copies of the *PKHD1* gene

* The PCR-amplified DNA is sequenced

- Normal DNA: A T C T A
- Mutant DNA: A T C A C

* The "test" sequence is then compared to the normal *PKHD1* sequence to determine whether there is a likely disease-causing change (mutation)
Objectives

Overview

ADPKD: key issues
• Data from clinical studies
• Diagnosis - radiologic; genetic
• Clinical issues and management

ARPKD: key issues
• Data from clinical studies
• Diagnosis - radiologic; genetic
  ➢ Clinical issues and management

ARPKD: Neonatal management

INCIDENCE: 1:20,000 live births
Typical birth at 34-36 wks gestation

RESPIRATORY
• Poor lung development
• 30% mortality

ARDS:
- Poor lung development
- 30% mortality

KIDNEY:
- Hyponatremia
- Decreased kidney function
- Very enlarged kidneys
- Hypertension

INCIDENCE: 1:20,000 live births
Typical birth at 34-36 wks gestation


© 2016 CTSI-CN | CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE AT CHILDREN'S NATIONAL | CTSICN.ORG
**ARPKD: Post-natal management**

**ININCIDENCE**: 1:20,000 live births  
Typical birth at 34-36 wks gestation

**RESPIRATORY**
- Poor lung development
- 30% mortality

**KIDNEY**
- Hyponatremia
- Decreased kidney function
- Very enlarged kidneys
- Hypertension

**LIVER**
- Portal hypertension
- Variceal bleeding
- Cholangitis

**ARPKD: Post-natal management**

**ININCIDENCE**: 1:20,000 live births  
Typical birth at 34-36 wks gestation

**RESPIRATORY**
- Poor lung development
- 30% mortality

**KIDNEY**
- Hyponatremia
- Decreased kidney function
- Very enlarged kidneys
- Hypertension


© 2016 CTSI-CN | CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE AT CHILDREN'S NATIONAL | CTSICN.ORG
ARPKD: Post-natal management

INCIDENCE: 1:20,000 live births
Typical birth at 34-36 wks gestation

LIVER
- Portal hypertension
- Variceal bleeding
- Cholangitis

RESPIRATORY
- Poor lung development
- 30% mortality

KIDNEY
- Hyponatremia
- Decreased kidney function
- Very enlarged kidneys
- Hypertension

FEEDING ISSUES
- Poor growth


© 2016 CTSI-CN | CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE AT CHILDREN'S NATIONAL | CTSICN.ORG
ARPKD: Post-natal management

**INCIDENCE:** 1:20,000 live births
Typical birth at 34-36 wks gestation

**LIVER**
- Portal hypertension
- Variceal bleeding
- Cholangitis

**KIDNEY**
- Hyponatremia
- Decreased kidney function
- Very enlarged kidneys
- Hypertension

**RESPIRATORY**
- Poor lung development
- 30% mortality

**INTRACRANIAL ANEURYSMS**

**FEEDING ISSUES**
- Poor growth


Summary

- PKD is a clinically significant disorder in children.
- Diagnostic strategies to distinguish ADPKD and ARPKD are improving. The usefulness of genetic testing has largely correlated with the strength of the clinical dx; but this is changing with new genetic tools.
- While the polycystic kidney diseases are clinically distinct, many disease manifestations are common. Current therapy for affected children focuses on supportive management.
## Acknowledgements

**UAB / Children’s National**
- Ravindra Boddu
- Renee Desmond
- Teresa Chacana
- Ludwine Messiaen
- Michal Mrug
- Amber O’Connor
- Chaozhe Yang
- Elena Gibson

**ARPKD Consortium**
- Gregory Germino – Johns Hopkins / NIH
- Stefan Somlo – Yale
- Luiz Onuchic – U Sao Paulo, Brazil
- Klaus Zerres – U Aachen, Germany

**CRISP Consortium**
- Vicente Torres – Mayo Clinic
- Arlene Chapman – Emory
- Jared Grantham – U Kansas
- Ty Bae – U Pittsburg

**ARPKD International Consensus Working Group (2014)**

**Funding:**
- NIDDK P30 HRFD Core Center
- Burroughs Wellcome Fund
- PKD Foundation
Correlation between ADPKD progression and GFR

Renal progression in ADPKD is marked by increases in total kidney volume (TKV); the decrease in GFR is inversely proportional to TKV.

MRI-based measurements are reliable and provide a valid marker of renal disease progression that detects significant changes over a relatively short period of time.

PKD1 and PKD2 patients differ with regard to rate of new cyst formation as opposed to rate of cyst growth and expansion.

The exponential rate of cyst growth in ADPKD indicates that early cyst formation, i.e. in utero, plays a critical role in disease progression.
Tolvaptan studies

STUDY:
- Phase 3, multicenter, double-blind, placebo-controlled 3-year trial
- 1445 patients, 18-50 years of age, total kidney volume (TKV) > 750 ml
- Primary outcome: annual rate change in TKV

RESULTS:
- TKV increased more slowly in the Rx group
- Slower decline in kidney function

CONCLUSIONS:
- Cyst growth and decline in kidney function progresses more slowly in Rx ADPKD pts than in controls, but adverse events are common.

ARPKD Clinical Trials: the Issues

- In ARPKD, the cystic lesion develops in utero, and progresses to cause massive expansion of kidney size/volume by birth.
- Kidney size/volume continues to increase until age 2-4 years and then the rate of growth slows due to the effects of secondary processes such as scarring and loss of nephrons.
- Kidney function is variable and not directly correlated with disease severity.
- No predictive markers of disease progression.
Challenges in ARPKD research

1. Define the natural history of ARPKD in patient subsets as a clinical platform for future therapeutic trials.

2. Fully characterize genetic-clinical correlations.

3. Identify prognostic markers - clinical/genetic.

4. Determine the clinical significance of missense mutations.

5. Investigate the impact of modifier genes.