Polycystic Kidney Disease or kidneys with cysts?

Cystic kidney disease: differential diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Autosomal Dominant Polycystic Kidney Disease (ADPKD)</td>
<td>1:1,000</td>
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<tr>
<td>Autosomal Recessive Polycystic Kidney Disease (ARPKD)</td>
<td>1:40,000</td>
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<tr>
<td>Medullary Cystic Kidney Disease (MCKD)</td>
<td>1:100,000</td>
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<tr>
<td>Nephronophthisis (NPHP)</td>
<td>1:100,000</td>
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<tr>
<td>Syndromic, with mental handicap</td>
<td>1:100,000</td>
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<tr>
<td>Joubert syndrome</td>
<td>1:100,000</td>
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<tr>
<td>Meckel-Gruber syndrome</td>
<td>1:140,000</td>
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<tr>
<td>Laurence-Moon/Bardet-Biedl syndrome</td>
<td>1:160,000</td>
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<tr>
<td>Systemic disease, various organs affected</td>
<td>1:50,000</td>
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<tr>
<td>Tuberous Sclerosis (TS)</td>
<td>1:100,000</td>
</tr>
<tr>
<td>Von Hippel-Lindau syndrome (VHL)</td>
<td>1:200,000</td>
</tr>
<tr>
<td>Benign simple cysts</td>
<td>&gt;50% above age 50</td>
</tr>
<tr>
<td>Medullary Sponge Kidney (MSK)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Chronic bilateral cysts</td>
<td>&gt;15%</td>
</tr>
<tr>
<td>Malignancy, cystic renal cell carcinoma</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Benign simple cysts

- Frequent chance finding on imaging (US / CT / MRI):
  - Age related: 25% of 40 year old and 50% of 50 year old
- Symptoms:
  - Usually none
  - Chronic pain; pressure on renal capsule or adjacent tissue
  - Pain and fever; cyst infection
- Characteristics:
  - No kidney enlargement
  - No destruction of normal kidney tissue
  - Kidney function impairment predisposes for simple cysts
- Treatment:
  - No treatment needed, no follow-up needed

Malignancy Cystic Renal Cell Carcinoma

- Prevalence:
  - Cystic RCC is 80% of all kidney related malignancies
- Symptoms:
  - Hematuria, flank pain and abdominal mass (all three: 10%)
  - Often a chance finding on imaging
- Diagnostics:
  - Ultrasound / CT / MRI → Bosniak classification
- Suspected cysts:
  - Thick irregular wall
  - Septa in cysts
  - Mass with various cavities
  - Enhancing of the lesion after IV-contrast
- Treatment:
  - Referral to urologist for nephrectomy (either partial or complete)
**Malignancy**

**Cystic Renal Cell Carcinoma**

**Bosniak classification of renal cysts**

- Thin wall without septa. Not enhancing with iv contrast. Diameter equal to that of water.
- Few thin septa, which may contain only fine calcifications.
- Well marginated cysts with a number of thin septa, with or without mild enhancement. Septa calcifications may be present.
- Enhancing soft tissue components after iv contrast adjacent to septa.

**Indeterminate cystic masses**

- Few thin septa, which may contain only fine calcifications.

**Thin wall without septa. Not enhancing with iv contrast. Density equal to that of water.**

**Few thin septa, which may contain only fine calcifications.**

**Well marginated cysts with a number of thin septa, with or without mild enhancement. Septa calcifications may be present.**

**Enhancing soft tissue components after iv contrast adjacent to septa.**

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**ADPKD**

- Autosomal Dominant Polycystic Kidney Disease
- 50% chance of inheritance by off-spring
- Most frequent heritable kidney disease (1:1.000)
- Mutation in either PKD1 or PKD2 gene
- Diagnosis often easy:
  - In most cases positive family history
  - However, 10% of cases has a de novo mutation
  - Genetic analysis is expensive and not 100% conclusive
  - Diagnosis is made especially on ultrasound / CT / MRI
    - Ravine criteria

**Ravine criteria (simplified)**

- Positive family history (90%)
  - 15-39 year: ≥ 3 (unilateral or bilateral) kidney cysts
  - 40-59 year: ≥ 2 cysts in each kidney
  - ≥ 60 year: ≥ 4 cysten in each kidney
- Negative family history (10%)
  - ≥ 10 cysts in each kidney and no indications of another polycystic kidney disease

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**The ADPKD phenotype**

- **Kidney related symptoms:**
  - Formation of numerous cysts, that compress renal tissue, causing renal function loss.
  - Need for dialysis in 70% of affected individuals at median age of 58 yr.
  - Intra-abdominal volume associated complaints (a.o. early satiety, weight loss, herniations).
  - Hypertension, pain, and cyst bleeding and infections.
- **Systemic complications:**
  - Cardiac valve abnormalities.
  - Increased prevalence cerebrovascular and aortic aneurysms.
  - Increase in cardiovascular mortality.
  - Liver cysts (sometimes need for liver transplant).

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**Images of ADPKD**
The course of kidney growth and kidney function decline

![Graph showing kidney growth and function decline over time.](image)

The effect of renoprotective treatments in specifically ADPKD

**Established renoprotective treatments in CKD:**
- Strict blood pressure control
- Inhibition of the Renin-Angiotensin-Aldosteron System
- Low protein diets

Not effective in ADPKD !!!

Epidemiological data

**Patients starting kidney replacement therapy according to cause of kidney failure**

![Graph showing incidence of different causes of kidney failure over time.](image)

Patient survival on Renal Replacement Therapy

![Graph showing patient survival on different types of renal replacement therapy.](image)

ADPKD patients in renal replacement therapy

**Numbers + costs in the European Union**

![Graph showing the increase in ADPKD patients in renal replacement therapy.](image)

Pathophysiology of a renal tubular cell

![Diagram illustrating the pathophysiology of a renal tubular cell.](image)
Tolvaptan improves disease progression
- Kidney volume growth and eGFR loss

N=1445 ADPKD, placebo or tolvaptan 90/30 mg
Age 18-50 yr, eCrCl>60 ml/min, TKV>750 mL

5.5 % per yr
2.8 % per yr
49%, p<0.001
2.7 ml/min/yr
2.7 ml/min/yr
26%, p<0.001

TEMPO study
Torres, Gansevoort et al
NEJM 2012

EMA: The indication for Jinarc® (tolvaptan)

JINARC® (tolvaptan) is indicated
- to slow the progression of cyst development and renal insufficiency in autosomal dominant polycystic kidney disease (ADPKD)
- in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Dutch Kidney Foundation (Investigator driven)</th>
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<tbody>
<tr>
<td>Patients</td>
<td>300 ADPKD, age 18 - 60 yr, eGFR 30 - 60 ml/min/1.73 m²</td>
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<tr>
<td>Intervention</td>
<td>Lanreotide 120 mg sc every 28 days or standard care</td>
</tr>
<tr>
<td>Duration</td>
<td>3 years</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Change in eGFR during treatment</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>- Change in total kidney volume - Change in total liver volume - Change in Quality of Life - Safety and tolerability</td>
</tr>
<tr>
<td>Coordination</td>
<td>4 UMCs (Groningen, Leiden, Nijmegen, Rotterdam)</td>
</tr>
<tr>
<td>Timeline</td>
<td>Start September 2012, closure September 2017</td>
</tr>
</tbody>
</table>

Somatostatin analogues for ADPKD

The Dutch DIPAK 1 Trial

Choice of the right patients
Kidney Volume to select patients for treatment

Rate of kidney function loss

Somatostatin analogues for PKD

Multicenter RCT, 3 yr FU
79 ADPKD patients with eGFR >40 ml/min*1.73m²
Octreotide 20 mg or placebo im every 28 days
ALADiN trial

Choosing the right patients
Kidney Volume to select patients for treatment

- 4.7
- 3.4
- 2.5
- 1.2
- 0.1

Note: no difference between males and females in average slope

1 Future eGFR decline (ml/min/1.73 m² per year) by subclass
Inrazabal et al JASN 2014

Summary

- The differential diagnosis of polycystic kidney disease is broad.
- Most cystic kidney disease are heritable and (very) rare. Most are easily recognized as part of a syndrome, affecting also other organs, and need specialized care.
- More common are:
  - Simple benign cysts and (pre)malignant cysts: need either no action, follow-up or nephrectomy
  - Bosniak classification helps making a distinction and dictates action to be taken
- Autosomal Dominant Polycystic Kidney Disease 1:1000
- 70% affected subjects develop ESRD at age ≈55 yr
- For long a disease without a treatment
- Recently the first effective drug was granted marketing authorization in the EU (JINARC®, a V2RA)
ADDITIONAL SLIDES

Heritable cystic kidney diseases

- **Autosomal recessive inheritance**
  
  - Prevalence: 1 in 40,000 life births
  
  - Variation in disease severity:
    - Newborns: Rapidly progressive disease, ~30% dies at very young age
    - Children: Less progressive disease with liver cirrhosis

- **Autosomal dominant inheritance**
  
  - Prevalence: 1 in 2,000

  - Diagnostics:
    - Typical findings on imaging
    - No liver cysts and/or no family history

  - Treatment:
    - As yet none, only supportive
    - In case of kidney failure: dialysis or kidney transplant

ARPKD

- **Autosomal Recessive Polycystic Kidney Disease**

- Prevalence of 1:40,000 life births

- Variation in disease severity:
  
  - Newborns: Rapidly progressive disease, ~30% dies at very young age
  
  - Children: Less progressive disease with liver cirrhosis

- Diagnostics:
  
  - Typical findings on imaging
  
  - No liver cysts and/or no family history

- Treatment:
  
  - As yet none, only supportive
  
  - In case of kidney failure: dialysis or kidney transplant

Images of ARPKD

Early stage versus later stage disease

Simple cysts, simple diagnostics ... ?
Variation within a family:
Age at reaching End-Stage Renal Disease

PKD1 families  PKD2 families

Age at ESRD (yr)

Variation within a family
Number of cysts

Female: 30 years
Affected sister: 28 years

Randomized Clinical Trials
Can renoprotection be achieved in ADPKD?

Standard blood pressure  Low blood pressure

Low blood pressure, -2.9 ml/min/1.73 m²/yr
Standard blood pressure, -3.0 ml/min/1.73 m²/yr
Difference, -0.1 ml/min/1.73 m²/yr (95% CI, -0.3 to 0.06)
P=0.55

HALT study: 558 ADPKD patients
Age 37 yr, TKV 1205 ml, eGFR 92 ml/min/1.73m²

ADPKD: Pathophysiology

Blanco et al, Am J Physiol 2013