Autosomal Dominant Polycystic Kidney Disease

John Sayer
Questions

Q1. I have polycystic kidney disease (PKD) but my parents seem to be unaffected – is this possible?
Questions

- Q2. I have PKD. Should my children be checked?
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- Q3. I have PKD and I am pregnant. Can my baby be tested?
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Q4. I sometimes have pain and bleeding from my polycystic kidneys. Can I have an operation?
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Q5. I want to have a transplant. Do my polycystic kidneys need to be removed?
Q6. I have had a kidney transplant. Can the PKD affect my transplant?
ADPKD

- Most common inherited kidney disorder
- 1 in 10 patients on dialysis / with transplant have ADPKD
- 1 in 400 - 1000 of population affected
- Males = females, occurs worldwide

- (Colour blindness 1 in 12 men; Cystic fibrosis 1 in 2500 (recessive))
Dominant pattern of inheritance
ADPKD

- Fluid filled cysts form in the kidney
- Slowly expand and replace normal healthy kidney tissue
- Kidney become 3 x bigger than normal

- Cysts occur in other organs too – esp Liver
Problems in ADPKD

- Symptoms include back or abdominal pain, recurrent urinary infections or blood in the urine, kidney stones and kidney failure.

- Nearly two thirds of adults with ADPKD will develop high blood pressure or hypertension.

- Early and effective treatment of hypertension is essential to minimise the risks of strokes or heart problems.

- Around 1 in 12 people with ADPKD will develop small brain aneurysms. These tend to occur in individuals with a family history of strokes.
Genetics

- Two genes: PKD1 and PKD2
- PKD1 Chrom 16 – 85% of cases
- PKD2 Chrom 4 – 15% of cases
What can I do to help my kidneys?

- **Avoid smoking**. Smoking damages the blood vessels in the kidneys and accelerates kidney damage.

- **Control your blood pressure**. High blood pressure is harmful to the kidneys and increases the risk of stroke and heart disease.

- **Watch your diet**. A balanced diet is important for everyone to stay healthy. It’s also important to limit how much salt you have in your diet because eating salt makes high blood pressure worse.

- **Take exercise**. Try to take regular exercise and be active. This helps prevent weight gain and can help to control blood pressure.

- **Drink plenty of water**. There is evidence to suggest that the body’s response to dehydration increases cyst growth. This response can be minimised by drinking plenty of water to stay hydrated.

- **Avoid NSAIDS**. Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medication commonly used to relieve pain, reduce inflammation and bring down a high temperature. They include ibuprofen and diclofenac. NSAIDs can cause scarring in the kidneys so it’s best to avoid them.
Diagnosis of ADPKD

- The most reliable way to diagnose ADPKD is by an ultrasound scan of the kidneys but you may first experience symptoms before a scan is done.
- Common early symptoms are back pain on either side of the abdomen, recurrent urinary infections or blood in the urine (haematuria). If there is a known family history of ADPKD, these symptoms may suggest the condition and a scan will usually confirm this.
- Other people may be diagnosed when found to have high blood pressure (or hypertension) or when having an ultrasound scan for some other reason, e.g. pregnancy.
- Usually, in someone at risk of inheriting ADPKD, the presence of cysts on both kidneys on a scan will suggest a positive diagnosis of ADPKD - as in the image above. However, as cysts tend to develop with age, in a young person or child the absence of cysts does not mean they have not inherited ADPKD.
Diagnosis

- **Family history**
- **Imaging**
- **Counselling before testing**
- **Benefits of a diagnosis** – certainty of diagnosis that could affect family planning, early detection and treatment of disease and complications, selection of genetically unaffected family members for living related donor transplantation
- **Disadvantages** - employment and insurance discrimination
- **Presymtomatic diagnosis in children** – adverse affects may out weigh benefits (removal of choice to know or not know, psychological, educational and career implications, insurance issues)
Diagnosis

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- Imaging

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Renal USS (Ravine criteria)

Positive diagnosis if
3 or more (unilateral or bilateral) renal cysts aged 15 to 39 y
2 or more cysts in each kidney in individuals aged 40 to 59 y,
4 or more cysts in each kidney is required for individuals ≥60 yr
To rule out ADPKD by USS

- < 2 renal cysts in at-risk individuals aged \( \geq 40 \) yr is sufficient to exclude the disease.
Renal USS in healthy

- 1 cyst age 15-29 0%
- 1 cyst age 30-49 1.7%
- 1 cysts 50-70 11.5%
- 1 cysts 70+ years 22.1%
Diagnosis – if no FH

- Clinical findings – bilateral renal enlargement and cysts, hepatic cysts
- Absence of features of rarer forms of cystic kidney disease (Tuberous sclerosis, VHL, BBS, OFD)
- Exclude acquired renal cystic disease – longstanding renal insufficiency, kidneys initially small (with time they may enlarge and resemble those of ADPKD)
Progression of cysts

- Size and number of the kidney cysts increases.
- Eventually the cysts begin to affect how the kidneys function, and chronic kidney disease (CKD) develops, which may result in kidney failure.
- Kidney failure is the most common worry for people with ADPKD. But not everyone develops kidney failure, and the rate that ADPKD progresses varies greatly even between close relatives. While half of people with ADPKD aged over 60 have kidney failure, a third of people reach age 70 without their kidneys failing completely. Some people with ADPKD can live a normal life, without needing kidney dialysis, despite losing up to 80% of their kidney function.
- It is currently impossible to predict who will develop kidney failure and when this will occur. However, your doctor can assess your rate of disease progression by regularly checking your kidney function.
Genetic testing

- Use when imaging equivocal
- Use when definitive diagnosis is required in a young pt (eg potential living related kidney donor).

- Linkage – markers around genes – requires several family members to be accurate
- Direct sequencing – more costly (PKD1 46 exons, PKD2 15 exons)
Hypertension

- Hypertension present in 50% of pts age 20-34 with ADPKD and normal renal fx
- 100% of pts with ESRF
- Activation of local intrarenal renin-angiotensin system
- BP often diagnosed late
- Early detection important as CVD is main cause of death
- Uncontrolled BP increases the risk for proteinuria, haematuria, decline in renal fx, morbidity and mortality from valvular heart disease and aneurysms
Pain

- 60% of adult pts report pain
- Acute pain – renal haemorrhage, passage of stones, utis
- Chronic flank pain in some pts
- Most haemorrhages resolve within 2-7 days
- 20% of pts have kidney stones
- Urinary stasis sec to distorted renal anatomy
- UTIs – usually enterobacteria
Renal Failure

- Highly variable
- Most have normal UEs until 4th-6th decade
- By time renal function deteriorating, kidneys usually large with little paranchyma
- GFR then decrease by 5 mL/min/year
- Risk factors for decline – males, blacks, haematuria before 30yrs, BP before 35 yrs
- Hyperlipidemia
- Smoking, use of NSAIDs
# eGFR and stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular Filtration Rate (GFR)</th>
<th>Kidney Function Deterioration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage (protein in urine) and normal GFR</td>
<td>More than 90</td>
<td>50% - 60%</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage and mild decrease in GFR</td>
<td>60 - 88</td>
<td>60% - 70%</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30 - 59</td>
<td>70% - 77.5%</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15 - 29</td>
<td>77.5% - 85%</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure—End Stage Renal Disease (dialysis or kidney transplant needed)</td>
<td>Less than 15</td>
<td>85% and above</td>
</tr>
<tr>
<td>GFR categories (mL/min/1.73 m²), description and range</td>
<td>ACR categories (mg/mmol), description and range</td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------------------------------</td>
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<tr>
<td>≥90 Normal and high</td>
<td>A1  Normal to mildly increased</td>
<td></td>
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<tr>
<td>60–89 Mild reduction related to normal range for a young adult</td>
<td>A2  Moderately increased</td>
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<tr>
<td>45–59 Mild–moderate reduction</td>
<td>A3  Severely increased</td>
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</tr>
<tr>
<td>30–44 Moderate–severe reduction</td>
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<tr>
<td>15–29 Severe reduction</td>
<td></td>
<td></td>
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<tr>
<td>&lt;15 Kidney failure</td>
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Increasing risk
Early onset ADPKD

- <1% of cases present in utero/neonatal
- Genetic studies used to distinguish between ARPKD
Extrarenal manifestations

- Polycystic liver disease – most common extra renal manifestation
- (can get just aut dom polycystic liver disease (PRKCSH, SEC63 mutations))
- Liver cysts are dilatations of biliary ductules and peribiliary glands
- Hepatic cysts larger in women – oestrogen receptors in cyst epithelial
Complications of liver cysts

- Cyst haemorrhage, infection, rupture, torsion
- MRI scan good imaging modality
Cysts in other organs

- Seminal vesicles (40%)
- Pancreas (5%)
- Arachnoid membrane (8%)
Vascular manifestations

- Intracranial aneurysms (6% with neg FH, 16% with +FH) Mean age of rupture 39yrs (vs 51yrs gen pop)
- Thoracic aortic and cervicocephalic artery dissections
- Coronary artery aneurysms
- Abnormal vasculature directly linked to mutations in PKD1 and 2
- Polycystin-1 and -2 expressed in vascular smooth muscle cells
Cardiac manifestations

- Mitral valve prolapse – 25% of pts
- Aortic root dilatation
Diverticular disease

- Colonic diverticulosis and diverticulitis more common in ESRF pts
Treatment

- Hypertension – tight BP control <130/80 important (HALT-PKD trial)
- ACE inhibitors / ARBs – renoprotective properties beyond BP control (HALT-PKD Trial)
Pain

- Exclude infection, stones, tumours
- Avoid long term nephrotoxic drugs
- Tricyclic antidepressants, pain clinic interventions (splanchnic nerve blockade)
- Surgical interventions – cyst aspiration under USS or CT guidance, sclerosing drugs
- Laproscopic surgery
- Nephrectomy in symptomatic patients with ESRD
Cyst haemorrhage

- Usually self limiting
- Conservative treatment – bed rest, analgesics, hydration
- For large bleeds consider CT or angiography – segmental arterial embolisation
Cyst infection

- Lipophilic antibiotics to penetrate cysts
- Nephrectomy may be indicated in ESRF for unresolved infection
Nephrolithiasis

- Ensure good fluid intake to prevent stones
End-stage renal disease

- Often do well on dialysis – better Hb (higher EPO concs) lower comorbidities
- PD ok, increased risk of hernia
- Transplantation is the treatment of choice
- Pre-transplant nephrectomy may be required for chronically infected cysts or frequent bleeding
Polycystic Liver disease

- If severe disease avoid oestrogens and compounds that promote cAMP accumulation (caffeine)
- Percutaneous cyst aspiration +/- sclerosis
Intracranial aneurysm

- Widespread presymptomatic screening is not indicated

- Indications for screening: FH of aneurysm or SAH, previous aneurysm rupture, preparation for major elective surgery, high risk occupations (e.g. airline pilots)

- MRI or CT angiogram
If an asymptomatic aneurysm is found – intervention depends on its size, site and morphology and history of SAH from another aneurysm, age, general health

Risk of new aneurysms or enlargement is very low if <7mm aneurysms, moderate if previous SAH

6-12 month screening, then less often if stable

Risk of new aneurysms after a negative initial study is 3% at 10 yrs – therefore re-screen after 5-10 yrs
New treatments

- Role of cAMP in cystogenesis – vasopressin V2 receptor antagonists reduce cAMP and reduce cyst formation in rodent models
- Tolvaptan – licence in Europe. Use in clinical trials in UK (Otsuka)
- Somatostatin – inhibits cAMP in kidney and liver – octreotide and lanreotide
- Activation of mTOR pathways in PKD – trials with sirolimus and everolimus
Questions

- Q1. I have polycystic kidney disease (PKD) but my parents seem to be unaffected – is this possible?

  Yes – in 10% of cases the disease appears spontaneously
Questions

- Q2. I have PKD. Should my children be checked?

- Will be discussed by Dr Lambert and Dr Winyard
Questions

- Q3. I have PKD and I am pregnant. Can my baby be tested?
  - Yes, it can be done using genetic testing.
Questions

Q4. I sometimes have pain and bleeding from my polycystic kidneys. Can I have an operation?

Operations to remove cysts are rarely helpful in the long run but in extreme cases the kidneys can be removed.
Questions

- Q5. I want to have a transplant. Do my polycystic kidneys need to be removed?

- Sometimes polycystic kidneys are so large that there is no room in the tummy for a transplant unless they are removed. Fortunately this is rare.
Questions

- Q6. I have had a kidney transplant. Can the PKD affect my transplant?

- No, your transplanted kidney will not have the abnormal gene, so it will not be affected.