Congenital, developmental & cystic diseases of the kidney

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Lecture outline

• Congenital and developmental diseases of the kidney

• Cystic diseases of the kidney
Congenital and developmental diseases of the kidney

- Agenesis
- Hypoplasia
- Ectopic kidneys
- Horseshoe kidney
**Agenesis**

*If bilateral*: incompatible with life

...usually seen in stillborn infants

...often associated with other defects (hypoplastic lungs...etc.)

*If unilateral*: compatible with life

...compensatory hypertrophy of the solitary kidney

...some patients: progressive glomerulosclerosis & chronic kidney disease...this is due to ECM deposition and epithelial/endothelial injury which resulted from the adaptive hemodynamic changes that accompanied the hypertrophy

**Hypoplasia**

= failure to develop to normal size

...more commonly unilateral

...if bilateral: renal failure in early childhood

...low birth weight infants are more at risk

...this is “true” hypoplasia

**Horseshoe kidneys**

= fusion of:

*upper poles...10% or *lower poles...90%

...continuous across the midline anterior to the great vessels

*This anomaly is found in 1 in 500 to 1000 autopsies

**Ectopic kidneys**

...usually not remarkable

...but risk of kinking/tortuosity of ureters...obstruction & bacterial infection
Cystic diseases of the kidney

• Hereditary, developmental or acquired

...defects in cilia-centrosome complex of tubular epithelial cells

Simple cysts

Autosomal recessive (childhood) polycystic kidney disease

Autosomal dominant (adult) polycystic kidney disease

Medullary diseases with cysts

Either in the medulla or in the corticomedullary junction

In the cortex

In the cortex and medulla
Simple cysts

• Clinically insignificant, commonly found incidental/postmortem lesions

• Multiple or single

• 1-5 cm in diameter...rarely as large as 10 cm

• Translucent glistening smooth membrane

• Lined by a single layer of cuboidal or flattened cuboidal epithelium...may be atrophic

• Usually confined to the cortex

• May present with hemorrhage & pain

The importance is in differentiating them from tumors...simple cysts have:
- smooth contours
- avascular
- fluid rather than solid tissue signal on ultrasonography

Tumors are irregular, more vascular, and could be a cystic tumor with a solid tissue (necrotic, hemorrhagic, etc.)
Simple cysts, cont’d…acquired cystic kidney disease

- In patients with end-stage renal disease...dialysis for many years
- Multiple
- In the cortex & the medulla
- May bleed...causing hematuria
- Risk for renal neoplasms...especially cystic ones

Most imp Cystic Renal Cell Carcinoma
Autosomal dominant (adult) polycystic kidney disease (ADPKD)

- Multiple cysts
- In both kidneys
- Ultimately destroy the intervening parenchyma
- Accounts for 10% of cases of chronic kidney disease
- In 85-90%: PKD1 gene on the short arm of chromosome 16 is defective
  ...encodes large and complex cell membrane–associated protein called
  polycystin-1...see the next 2 slides
ADPKD, pathogenesis

• Polycystin-1 normally localizes to the primary cilium of tubular cells

• Cilia serve as mechanosensors of fluid flow

• Polycystin mutations will cause defects in mechanosensing

• Abnormal signal transduction...calcium influx

• Dysregulation of cell polarity, proliferation, cell–cell and cell–matrix adhesion, & secretion from the tubular epithelial cells

• Cyst formation
  ...the cysts progressively enlarge overtime

Also: inflammation & fibrosis
• Germline mutations of the *PKD1* gene are present in all renal tubular cells of affected individuals...but: cysts develop in only some tubules

...which means: a second “somatic hit” is required for cyst development
ADPKD, pathogenesis...cont’d

• *PKD2* gene
  ...10-15% of the cases
  ...on chromosome 4, encodes **polycystin-2**

  ...a calcium-permeable membrane channel
  ...also localized to cilia
  ...acts together with polycystin-1 to form heterodimer
  ...so: a defect in any of the two will cause the same result

  ...However, *PKD2* mutations: slower disease progression
ADPKD, morphology

- very large...may reach 4 kg for each kidney
- palpable
- may be formed solely of cysts...each 3-4 cm
- turbid, clear or hemorrhagic fluid
- cysts may arise at any level from tubules to collecting ducts
- variable, often atrophic lining
- occasionally, Bowman’s capsules are involved in the cyst formation, and in these cases glomerular tufts may be seen within the cystic space
- some normal parenchyma may be dispersed among the cysts
- evidence of superimposed hypertension or infection is common
- asymptomatic liver cysts also occur in one-third of patients

The lining of the cysts is variable, some of which are cuboidal, others are flattened (according to the origin), and as a result of fluid pressure inside of them, they are often atrophic.

The normal weight of the kidney is:
125-175 g in the males
115-155 g in females
ADPKD, clinical features

• Usually does not produce symptoms until the fourth decade of life

• The most common presenting complaint is flank pain or a heavy, dragging sensation

• Acute distention of a cyst, either by intracystic hemorrhage or by obstruction, may cause excruciating pain

• Sometimes attention is first drawn to the lesion on palpation of an abdominal mass

• Intermittent gross hematuria commonly occurs

• The most important: hypertension (75% of patients) & infection
ADPKD, clinical features...cont’d

• Saccular aneurysms of the circle of Willis...10-30% of patients

• More favorable than with most chronic kidney diseases...although it is ultimately fatal

• Slow progression
  ...end-stage renal disease occurs at about 50 years of age
  ...even nearly normal life spans are reported

• Treatment: renal transplantation

• Death: usually due to uremia or HTN

Uremia means abnormally elevated levels of urea plus creatinine in the blood with symptoms of coma, seizures, etc, so fatal
Azotemia means abnormally elevated levels of urea and creatinine in the blood but without symptoms
Autosomal recessive (childhood) polycystic kidney disease (ARPKD)

• Rare

• Subcategories:
  - Perinatal
  - Neonatal
  - Infantile
  - Juvenile

  Perinatal means at the birth, neonatal means in the first month of life

• The defect is in \textit{PKHD1} gene, coding for a membrane receptor protein called fibrocystin

  The letter H stands for the hepatic involvements which are common

• Fibrocystin is found in cilia in tubular epithelial cells...unknown function
ARPKD, morphology

- Numerous small cysts in the cortex and medulla...sponge-like appearance
- Uniform lining of cuboidal cells, reflecting their origin from the collecting tubules
- Invariably bilateral
- Multiple epithelium-lined liver cysts and proliferation of portal bile ducts...in almost all cases
ARPKD, clinical features

• Serious manifestations usually are present at birth

• Young infants may die quickly from hepatic or renal failure

• Patients who survive infancy develop liver cirrhosis...congenital hepatic fibrosis

Hepatic Fibrosis is before cirrhosis, and these vary between the the different subcategories of ARPKD
Medullary diseases with cysts

• 2 major types of cystic disease affecting the medulla:
  
  - medullary sponge kidney
    ...relatively common
    ...usually innocuous
    ...occasionally associated with nephrolithiasis
  
  - nephronophthisis-medullary cystic disease complex
    ...almost always associated with renal dysfunction
Nephronophthisis-medullary cystic disease complex

• Usually begins in childhood

• 4 variants:
  - Infantile
  - Juvenile...the most common
  - Adolescent nephronophthisis
  - Medullary cystic disease developing later in adult life
Nephronophthisis-medullary cystic disease complex
...juvenile form

• 15-20% have extrarenal manifestations:
  ...retinal abnormalities: retinitis pigmentosa and even early onset blindness
  ...oculomotor apraxia
  ...mental retardation
  ...cerebellar malformations
  ...liver fibrosis

- a genetic disorder of the eyes that causes loss of vision. Symptoms include trouble seeing at night and decreased peripheral vision (side vision)

- also known as Cogan ocular motor apraxia or saccadic initiation failure (SIF) is the absence or defect of controlled, voluntary, and purposeful eye movement (NO motor planing)
Nephronophthisis-medullary cystic disease complex, pathogenesis

- Many affected genes either autosomal dominant or recessive
- At least nine gene loci (NHP1 to NHP9) have been identified for the autosomal recessive forms of the nephronophthisis complex
- The majority of these genes encode proteins that are components of epithelial cilia
Nephronophthisis-medullary cystic disease complex, morphology

• Small contracted kidneys

• Numerous small cysts lined by flattened or cuboidal epithelium are present...typically at the corticomedullary junction

• Chronic tubulointerstitial nephritis with tubular atrophy and thickened tubular basement membranes and progressive interstitial fibrosis...nonspecific

Can be seen in many kidney diseases

Always remember that the chronic changes in the kidney are: Tubular Atrophy, Thickening of the tubular basement membrane, and Interstitial fibrosis. These changes are nonspecific
Nephronophthisis-mediullary cystic disease complex, clinical features

Clinical Features
The initial manifestations are usually polyuria and polydipsia, a consequence of diminished tubular function. Progression to end-stage renal disease ensues over a 5- to 10-year period. The disease is difficult to diagnose because there are no serologic markers, and the cysts may be too small to be seen with radiologic imaging. Adding to this difficulty, cysts may not be apparent on renal biopsy if the corticomedullary junction is not well sampled. A positive family history and unexplained chronic renal failure in young patients should lead to suspicion of nephronophthisis.
Thank You