Hereditary Tubulointerstitial Kidney Diseases

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Tubulointerstitial diseases can be visually esthetic

Primary chronic tubulointerstitial diseases
Limited spectrum of injury despite numerous etiologies

Etiologies
- Obstruction/chronic infection
- Autoimmune
- Nephrotoxic
- Light chain / paraprotein-related disease
- Hereditary tubulointerstitial disease
Hereditary primary tubulointerstitial diseases
- Hereditary chronic tubulointerstitial nephritis
- Nephronophthisis
- Medullary cystic kidney disease/autosomal dominant tubulointerstitial disease
- Hereditary crystalline nephropathies
- Cystinosis
- Primary hyperoxaluria
- 2,8 dihydroadeninuria
- Hereditary tubular transport nephropathies
- Dent's disease
- Lowe's oculo-cerebral-renal syndrome
- Bartter's syndrome
- Miscellaneous other hereditary tubulointerstitial kidney diseases
- Systemic karyomegaly
- Mitochondrial cytopathies

Primary chronic tubulointerstitial disease
Working definition:
"Disproportionate" tubulointerstitial injury compared to glomerular injury
Late stage glomerulosclerosis may catch up

Nephronophthisis / medullary cystic kidney disease
Strategy
- Evolution of terminology
- Pathogenesis
- Clinical features
- Pathologic features
  - Gross
  - Microscopic

NPHP / MCKD
Smith & Graham, Congenital medullary cysts of the kidney
Am J Dis Child 369, 1945
Title captured its major gross finding
9 year-old girl
Autopsy findings and clinical course
"Rare congenital lesion...with intractable anemia...severe azotemia...despite minimal urinary findings"

NPHP / MCKD
Fanconi VG, et al. Die familiäre juvenile nephronophthisis
Helvet Paediat Acta 6:1, 1951
Coined the term "familial juvenile nephronophthisis"
Greek for disintegration of nephrons
"phthisis" (tisis) - to decay
Captured its major histologic features
2 families - multiple children developed renal failure by age 6
Polyuria, polydipsia and nocturia
Hypertension and significant proteinuria absent

NPHP / MCKD
Goldman et al. Hereditary occurrence of cystic disease of the renal medulla
Autopsy reports on 6 / renal biopsy on 2
Drew attention to autosomal dominance of some cases
Traced 60 family members through 5 generations
14 died of renal disease -- average 25 yrs. old
NPHP / MCKD

Chamberlin, et al. Juvenile nephronophthisis and medullary cystic kidney disease
Mayo Clinic Proc 52:485, 1977

Literature review
7 cases NPHP & 33 cases MCKD

Argued for their separation into
NPHP - AR childhood onset
MCKD - AD adult onset

Early 21st century – pathogenesis defined
AR Nephronophthisis - recognized as a ciliopathy in 2003
AD MCKD - 4 mutations identified
- Uromodulin
- Mucin-1
- Renin
- HNF-1ß
- Other(s) remain to be identified

Ekici AB, et al. in 2014 - proposed renaming MCKD
Autosomal dominant tubulointerstitial disease

Hereditary chronic tubulointerstitial diseases are rare
NPHP - 1.1 per 1,000,000 - US
- 1 per 50,000 - Canada

ARPKD - 1 per 20-50,000
VHL - 1 per 35,000
TSC 1 per 7,000
ADPKD - 1 per 500-1,000

ADTID-UMOD - 1 per 700,000-1,000,000
ADTID-MUC7 - 100 families reported in US by 2015
ADTID-REN - 14 families reported by 2005
ADTID-HNF1ß
- Most common cause of MODY
- 10-30% of Congenital anomalies of the kidney and urinary tract in children and adults
- Chronic tubulointerstitial nephritis - very rare

Nephronophthisis
- Most common genetic cause for ESKD in the first 3 decades of life
- 10-25% of children with chronic renal failure
- Syndromic NPHP (extra-renal disease) in 10-20%
- Presentation
  - Concentration defect with polydipsia, polyuria and enuresis
  - Severe anemia
  - Little proteinuria or hematuria
  - Lack of hypertension due to salt wasting
  - Later develop
  - Growth retardation
  - Renal osteodystrophy
  - Progressive renal failure by age 30
### NPHP - 3 clinical phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age onset</th>
<th>Kidney size</th>
<th>Cyst location</th>
<th>Glom. cyst</th>
<th>TBM changes</th>
<th>Cortical inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile</td>
<td>&lt; 4 yrs (can be antenatal)</td>
<td>Normal to enlarged</td>
<td>Cortex and medulla</td>
<td>Present</td>
<td>Absent</td>
<td>Mild</td>
</tr>
<tr>
<td>Juvenile</td>
<td>13 yrs</td>
<td>Small to normal</td>
<td>Cortico-medullary</td>
<td>Absent</td>
<td>Present</td>
<td>Prominent</td>
</tr>
<tr>
<td>Adolescent</td>
<td>19 yrs</td>
<td>Small to normal</td>
<td>Cortical medullary</td>
<td>Absent</td>
<td>Present</td>
<td>Prominent</td>
</tr>
</tbody>
</table>

### NPHP - 20 nephrocystin mutations identified

<table>
<thead>
<tr>
<th>Most common mutations</th>
</tr>
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<tbody>
<tr>
<td>Gene</td>
</tr>
<tr>
<td>NPHP1</td>
</tr>
<tr>
<td>NPHP4</td>
</tr>
<tr>
<td>CEP290</td>
</tr>
<tr>
<td>IQCB1</td>
</tr>
<tr>
<td>TMEM67</td>
</tr>
<tr>
<td>INVS</td>
</tr>
<tr>
<td>NPHP3</td>
</tr>
</tbody>
</table>

### NPHP - a CTIN that may form cysts

- **Dotland definition of a cyst:**
  - Any closed cavity or sac (diverticulum) lined by epithelium
- Reported incidence of cysts is affected by:
  - Application of the term cyst
  - Tubular ectasia called cysts (Brouhard et al 1977)
  - Microcysts visible in tissue sections
  - Macrocyts visible on imaging or grossly visible
  - Imaging modalities and sensitivities
  - Clinical duration – cysts increase over time
  - NPHP 50-70% have cysts at autopsy

### NPHP - pathology

- **Ivemark BI, et al.**
  - Juvenile nephronophthisis
  - Acta pediatr ica 49:480, 1960
- 2 autopsy cases - 12 yrs. old
  - Kidney wts: 40 gms. / 60 gms.
  - Microcysts in cortex
  - Macrocysts in medulla
  - Medullary ray radial tubular ectasia
  - Medullary cysts
  - Loop of Henle residue
  - Collecting duct
NPHP - microdissection
3 autopsies
Early microcystic changes
- Diverticuli descending limbs of Henle
- Tubular "microcysts" - distal tubules and collecting ducts

NPHP - LM, IF and EM
9 NPHP pts - 3 autopsies and 6 biopsies
Reviewed 95 well-documented cases
68 autopsies and 27 biopsies
68 autopsies
Cortical cysts
16/68 cases – 18%
Medullary cysts
44/68 cases – 65%

Nephronophthisis - ESK but no cysts

Nephronophthisis - medullary cysts

Syndromic NPHP - renal-retinal dysplasia

Medullary cysts - differential diagnosis
- Nephronophthisis
- Autosomal dominant tubulointerstitial disease
- Autosomal dominant polycystic kidney disease, early onset
- Autosomal recessive polycystic kidney disease, childhood form
- Acquired cystic kidney disease
- Medullary sponge kidney
Autosomal dominant polycystic kidney disease, early onset

Acquired cystic kidney disease

Acquired cystic kidney disease

Autosomal recessive polycystic kidney disease

ARPKD - childhood onset

Medullary sponge kidney

- Developmental disease with bilateral collecting duct cysts
- Usually sporadic, rarely autosomal dominant
- Isolated to syndromic disease
- Hypercaluria, concentration and acidification defects, hematuria
- Moderate risk of CKD
- Nephrocalcinosis and nephrolithiasis
Medullary sponge kidney
Nephrocalcinosis and Nephrolithiasis

NPHP - chronic inflammation and fibrosis with glomerular sparing

NPHP - TBM replication and periglomerular fibrosis

Periglomerular fibrosis and TBM splitting - nonspecific findings
Examples:
- Arterial nephrosclerosis
- Chronic allograft nephropathy
- Diabetic glomerulopathy

Infantile NPHP with congenital hepatic fibrosis
NPHP2 / occasionally NPHP3 mutations

NPHP clinical phenotype - 7-year old
Polyuria/polydipsia, CRF, no proteinuria or hematuria
Autosomal dominant tubulointerstitial disease

KDIGO classification [Kidney Int 88:676, 2015]

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Same</th>
<th>Previous terminologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADTKD-UMOD</td>
<td>LMOD</td>
<td>Medullary cystic kidney disease Type 2 Uromodulin kidney disease Familial hyperuricemic nephropathy type 1 Uromodulin storage disease</td>
</tr>
<tr>
<td>ADTKD-MUC1</td>
<td>MUC1</td>
<td>Medullary cystic kidney disease type 1 Mucin-1 kidney disease</td>
</tr>
<tr>
<td>ADTKD-RENI</td>
<td>RENI</td>
<td>Renal hyperuricemic nephropathy type 2</td>
</tr>
<tr>
<td>ADTKD-HNFB1β</td>
<td>HNFB1β</td>
<td>Nephron-renal diabetes of the young type 1 Renal cyst and diabetes syndrome</td>
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<tr>
<td>ADTKD-NDG</td>
<td>NDG</td>
<td></td>
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</table>

KDIGO Classification

Recommended terminology
- ADTKD - UMOD
- ADTKD - MUC1
- ADTKD - RENI
- ADTKD - HNFB1β

Terminology for this talk
- Uromodulin kidney disease
- Mucin-1 kidney disease
- Renin kidney disease
- HNFB-1β kidney disease
ADTINs differ in pathogenesis

- Uromodulin kidney disease
- Mucin-1 kidney disease
- Renin kidney disease
- HNFB-1β kidney disease
- TALH - protein-folding disorder, impairs intracellular trafficking, retention in ER
- DT/CD - truncated protein lacks transmembrane and intracellular domain
- JGA - heterozygous mutation leads to decreased renin production
- Transcription factor primarily expressed in kidney, pancreas and liver essential for embryogenesis

Uromodulin kidney disease

202 patients / 74 families
- Hyperuricemia 91%
- Gout 48%
- 59 different UROM mutations
- ESRD earlier in males
- Onset ESRD affected by mutation

109 patients from 45 families
37% renal cysts

Mucin-1 kidney disease

206 patients / 24 families
95 of 186 tested had MUC1 mutations
Broad range of ESRD -16 to 81 years
Gout 24%
Mucin-1 kidney disease


Renal cysts
- 1 cyst in 13%
- 2 or more cysts in 12%
- Medullary cysts - 0%

Renal biopsies in 34 patients (pathology not shown)
- 34 CTIN
- 4 of 34 microcysts

Renin kidney disease

Heterozygous mutation of REN - decreased renin production in JGA
- Chronic tubulointerstitial nephritis
- Homozygous or compound heterozygous mutation of REN
- Renal tubular dysgenesis

Clinical features CTIN
- Hypoproliferative anemia - low reticulocyte count relative to low hemoglobin and elevated erythropoietin
- May affect children as early as 1 year
- Some have polyuria and enuresis
- Hyperuricemia in childhood and gout as adults
- Some patients have low blood pressure or elevated potassium
- Slowly progressive renal failure - ESRD in 4-6th decade

HNF-1β kidney disease

HNF1β transcription factor: organogenesis of kidney, urinary tract, liver, pancreas

Three clinical presentations
1. Maturity-onset diabetes mellitus of the young (MODY)
   - HNF1β most common cause
   - Pancreatic hypoplasia or agenesis
2. Congenital anomalies of kidney and urinary tract (CAKUT)
   - 10-30% of cases in children and adults
3. Slowly progressive renal failure in adults due to CTIN
   - Average onset 24 years
   - Concentrating defect
   - Low magnesium

HNF-1β kidney disease


27 adults from 20 families
- Hypokalemia 11/24 / Hypomagnesemia 10/16
- Fanconi syndrome 2/27
- Abnormal liver functions 8/21
- Diabetes 13/27 including 11 with MODY
- Cysts 15/24
- Solitary kidney 5/24
- Genital abnormalities in 5/13 females and infertility in 2/14 males

ADTIN - features the 4 types have in common

- Autosomal dominant
- Many family members affected over multiple generations
- Age of onset/ rate of progression varies between and within families
- Unexplained chronic kidney disease
- Concentrating defect – polyuria, polydipsia, nocturia, enuresis in children
- Hyperuricemia or gout
- Little or no proteinuria or hematuria
- Cysts commonly present but usually late in disease and not always medullary
- Biopsy not recommended
- Genetic testing recommended

ADTID, of some type

Adult with “MCKD”

Bilateral nephrectomy for massive urinary tract hemorrhage
Uromodulin kidney disease
3 families with "AD-MCKD"
Chronic tubulointerstitial nephritis
Uromodulin aggregates retained within TALH endoplasmic reticulum

Uromodulin kidney disease

Uromodulin kidney disease
18 year-old female
- Creatinine 1.8/ no protein or blood
- Uric acid 11.1 mg/dl, history of gout
- US - bilateral small cysts
- Father - ESRD

Uromodulin kidney disease
Biopsy findings:
Chronic tubulointerstitial nephritis
Microcysts in 12%
Images: Helen Liapis / from Colvin’s Text
Ekici et al Kidney Int 86:589, 2014

Mucin-1 kidney disease
Biopsy findings:
Chronic tubulointerstitial nephritis
Images: Helen Liapis / from Colvin’s Text
Ekici et al Kidney Int 86:589, 2014

Renin kidney disease
Chronic tubulointerstitial nephritis
JGA normal appearing
No renal cysts
Images - Lynn Cornell / Colvin’s Text
Renin kidney disease

Zivna et al.
Am J Hum Genet 85: 204, 2009

Chronic TIN
Renin and prorenin markedly decreased to absent in JGA

Renin - homozygous or compound heterozygous mutation

Renal tubular dysgenesis
- Failure of proximal tubule differentiation
- Antenatal or neonatal death

Renal tubular dysgenesis
1. Homozygous or compound heterozygous mutation of renin or other angiotensin system genes
2. Complications of maternal drug use
   - Angiotensin converting enzyme inhibitors
   - Angiotensin type II receptor antagonists
   - Non steroidal anti-inflammatory drugs
3. Twin-twin transfusion syndrome

HNF-1β kidney disease

Pathology – 2 broad categories
Cysts and cystic kidney disease - 60-80%
Chronic tubulointerstitial nephritis - ?

No genotype-clinical phenotype correlations

HNF1β Kidney disease

CAKUT – major malformations
Renal agenesis
Renal dysplasia
Renal hypoplasia
Renal fusion, ectopia and duplication
Uretal-pelvic junction and uretero-vesical junction obstruction
Vesicoureteral reflux
Ureteral duplication and ectopia, and ureteroceles
Bladder extrophy, persistent cloaca, rectal-vesicle fistula
Urethral atresia and posterior urethral valve

Glomerular cystic kidney disease

Classification of GCK
Sporadic glomerulocystic kidney disease
Hereditary glomerulocystic kidney diseases
Autosomal dominant GCKD due to UROM mutation
Familial hypoplastic GCKD due to HNF1B mutation
Hereditary GCKD, nos
Glomerular cysts associated with hereditary syndromes:
Syndromic and non-syndromic renal dysplasia

HNF-1β Kidney disease

CTIN - the least common renal manifestation

Heidet L, et al. Spectrum of HNF1B mutations

75 heterozygous HNF1B mutations
- 12 of 75 had hyperuricemia or gout!
ADTID kidney disease, nos
28 year-old white male
- Cr. 2.2, concentrating defect
- US normal size kidneys / no cysts
- Father – carries a dx of MCKD
- Grandfather - ERSD unknown cause

Diagnosis of ADTIN
ADTID phenotype
- Autosomal dominant family history of CKD - multiple generations affected
- Concentrating defect, anemia and elevated uric acid (UROM and REN)
- Unexplained CKD with little or no proteinuria/hematuria
Exclude:
- Drugs, nephrotoxins
- Lower urinary tract obstruction +/or infection
- Cysts absent or infrequent early on
Genetic testing strategy (from GeneReview)
- UROM if gout is a significant portion of the disease
- REN if anemia, hyperkalemia or low blood pressure are an issue
- MUC1 if gout, anemia and hyperkalemia are absent
- HNF1β if low magnesium, cysts or diabetes are present

ADTIN - obstacles to the diagnosis
Autosomal dominant family history absent
- De novo mutation
- Early death of affected parent
- Late onset of disease in affected parent
- Alternative paternity or maternity of affected parent
Lack of clinical or morphologic phenotype due to a 2nd disease process
- Diabetes/metabolic syndrome +/- hyperuricemia or gout
- Smoking
- Hypertension
- NSAIDS, other ingestions

NPHP and ADTIDs - conclusions
A group of rare (possibly underdiagnosed) disorders with overlapping clinical and morphologic features
Vary in inheritance - AR, AD
Differ in pathogenesis
NPHP – ciliopathy
ADTID - mutation of one of several proteins involved in diverse functional and/or developmental activities

NPHP and ADTIDs - conclusions
Most form cysts but these appear late
Renal biopsy shows
- Non-specific CTIN in most cases
- Objective findings: UROM deposits, ↓Renin in JGA

Renal biopsy is not recommended, or rarely performed, which deprives us of...
- Opportunity to acquire diagnostic experience
- Learn the nuances of their earliest stages
- Make phenotypic-genotypic correlations as new mutations are identified

Genetic testing is recommended
Mutation responsible in many cases yet to be identified
UROM, REN and MUC11 Registries – abileyer@wfubmc.edu

Hereditary CTIDs - NPHP and ADTIDs
A diagnostic black hole hopefully slightly less deep?
Thank you.

<table>
<thead>
<tr>
<th>NPHP and ADTID - comparison of major clinical and pathology features</th>
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<tbody>
<tr>
<td>Mutation</td>
</tr>
<tr>
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<tr>
<td>NPHP</td>
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<tr>
<td>ADTID</td>
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<tr>
<td>UROM</td>
</tr>
<tr>
<td>MUC1</td>
</tr>
<tr>
<td>REN</td>
</tr>
<tr>
<td>HNF1B</td>
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<table>
<thead>
<tr>
<th>14 male Cr. 7</th>
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<table>
<thead>
<tr>
<th>NPHP</th>
<th>ADTIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>common</td>
</tr>
<tr>
<td>Family history</td>
<td>Single generation (sibs)</td>
</tr>
<tr>
<td>Average age onset</td>
<td>6 years</td>
</tr>
<tr>
<td>Average ESRD</td>
<td>13 years</td>
</tr>
<tr>
<td>Cysts</td>
<td>–/+ (late finding)</td>
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<tr>
<td>Syndromic</td>
<td>10-20%</td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td>Hypercalcuria Anemia</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Polyuria/polydipsia</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Progressive CKD</td>
</tr>
<tr>
<td>Glomerular findings</td>
<td>None to minimal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>14 male - 57 of 65 GS</th>
</tr>
</thead>
</table>

| 14 male - multiple UTI, hypertension and >1gm prot. |
NPHP – 19 mutations identified
30-40% of cases - NPHP1 accounts for 20% of cases


Autosomal dominant tubulointerstitial disease
Differentiating features

<table>
<thead>
<tr>
<th>Feature</th>
<th>UMOD</th>
<th>MUC1</th>
<th>REN</th>
<th>HNF1</th>
</tr>
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<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Risk of AKI in childhood</td>
<td>Low-normal BP</td>
<td>Risk of cystic kidney disease</td>
<td>Renal cysts and diabetes</td>
<td>Renal abnormalities</td>
</tr>
<tr>
<td>Presentations</td>
<td>Recent renal failure 5-60 years</td>
<td>Cyst 3-7th decade</td>
<td>Early onset Cyst 4-6th decade</td>
<td>Presents in childhood</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia and gout</td>
<td>Hyperuricemia especially in males</td>
<td>Hyenaemia</td>
<td>Pancreatic insufficiency</td>
<td></td>
</tr>
</tbody>
</table>

Importance of the correct diagnosis of NPHP and ADTID
- Identify potential kidney donors
- Avoid need for biopsy in other family members
- Provide prognostic and family counseling information
- Allow family members to participate in, or support, research for their rare condition
- Some have treatment options, REN kidney disease

NPHP
Cohen A and Hoyer RJ
Nephronophthisis: a primary tubular basement membrane defect.
Lab Invest 55: 564, 1986
4 patients: 10-18 years old
- TBM thinning and splitting
- Morphologically analogous to Alport syndrome

Hereditary tubulointerstitial nephritis
1962 - MB Strauss
18 cases (prior to that only 7 cases reported)
- Age 8-56 year
- Hg 4-11.5 gm
- Specific gravity < 1.099
- Average serum calcium 7.2 mg/dl
- “Renal rickets” in young patients
- Family history of renal disease present in 2 of 18 patients
(Likely includes both nephronophthisis and medullary cystic kidney disease)
Infantile nephronophthisis
NPHP2 / occasionally NPHP3 mutations


Mixed epithelial and stromal tumor family

– 10 patients
– ESRD by 22 months
– 10 renal bxs, 4 autopsy kidneys
– 6/10 Congenital hepatic fibrosis

ADPKD in children may differ form adults

Medullary dysplasia
Prune belly syndrome

Fetus - elective termination
Family history of NPHP