CAKUT in the 21st Century

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IPNA – AfSPN Junior Master Class
CAKUT Roadmap

- Epidemiology/Significance
- Mechanisms
- Clinical presentations
- Outcomes
Objectives

1. Describe the Epidemiology and Significance of CAKUT
2. Identify the Typical Clinical Presentations for Children with CAKUT
3. Define the Most Common Mechanisms for Development of CAKUT
4. Discuss the Present-Day Outcomes for Children with CAKUT

Most common cause ESKD in children

Profoundly affects Quality of Life in these children

Significant interventions available to preserve renal function
1-day old female

- 2.1 kg, 31 weeks gestation, history of amnioinfusions, suspected L MCDK and R hyperechoic kidney. Anuric. Transferred for urgent nephrology & urology consultation
R cystic dysplasia, L hydronephrosis (?UPJO) with urinoma


9 yo: GFR 74 ml/min/1.73 M2; normal intelligence, good QOL
Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

- Common (3-6 per 1000 live births);
- 23% of overall birth defects
- Congenital Defects
  - can be bilateral or unilateral
  - different ones often coexist in an individual
  - most common is VUR
CAKUT and Pediatric ESKD

<table>
<thead>
<tr>
<th>Distribution by diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive uropathy</td>
<td>1,385</td>
</tr>
<tr>
<td>Aplastic/hypoplastic/dysplastic kidney</td>
<td>1,125</td>
</tr>
<tr>
<td>Other</td>
<td>913</td>
</tr>
<tr>
<td>FSGS</td>
<td>557</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>536</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>257</td>
</tr>
<tr>
<td>Prune belly</td>
<td>185</td>
</tr>
</tbody>
</table>

40-50% of Pediatric ESKD

NAPRTCS, 2008
CAKUT Causes and Clinical Presentations

- 25% of cases have a **genetic** basis
- Also can be due to **environmental** factors
  - Micronutrients (e.g., folate, vitamin A deficiency)
  - Maternal diabetes
  - ACEi
  - *In vitro* fertilization

**Clinical presentations:**
- Abnormal pre or postnatal imaging
- UTI
- Renal insufficiency/poor growth
- Abnormal bladder function
- Abdominal mass/pain
The anatomic spectrum of CAKUT

Kidney abnormalities
- Hypoplasia/dysplasia
- Agenesis
- Multicystic dysplasia

Ureteral abnormalities
- Vesicoureteral reflux
- Duplex collecting system
- Ureteropelvic junction obstruction

Lower urinary tract abnormality
- Posterior urethral valves
Gupta and Murugupooopathy (2020) CJASN
8 year old Nepali boy with *E. coli* urosepsis, history of bowel and bladder dysfunction
VCUG
Fast forward to 2020

Serum Cr (mg/dl)

- 11/1/2011
- 11/1/2012
- 11/1/2013
- 11/1/2014
- 11/1/2015
- 11/1/2016
- 11/1/2017
- 11/1/2018
- 11/1/2019
CAKUT typically arises from combination of genetic & environmental factors but **monogenic disorders** explain some CAKUT cases.  
15% of all CAKUT explained by Heterozygous dominant gene mutations in 2 transcription factors: *HNF1B* and *PAX2*
Nephrogenesis occurs between wks 6-36 of gestation – final outcome = 200,000 – 2,000,000 nephrons/kidney – tremendous variability
As Always - Timing is Everything!

...And severe defects arise earlier in development

Gupta and Murugupoopathy (2020) CJASN
“Solved” vs. Unsolved Causes of ESRD

- 68 patients with ESRD underwent WES
- 40% had causative mutation
- CAKUT accounted for 56% patients with ESRD
- Of these, 29% had causative mutation

Mann et al. (2019) JASN
Utilizing Human Organoids to Study Development and CAKUT
Genome Editing: Confer/Correct CAKUT in Organoids
Additive effect of LBW, SGA, prematurity on CKD incidence

Gjerde (2020) CJASN
CAKUT Outcomes

CAKUT Outcomes - PUV

• 1/5000-1/8000 male births
• Partial bladder outlet obstruction
• 15-20% will progress to ESKD during childhood

Who will need renal replacement therapy?
RRT in a Birth Cohort of Boys with PUV

- 273 cases
- 5 institutions
- 1995-2004

McLeod et al (2018) *Pediatrics*

CKD progression continues into adulthood
Predictors of ESKD in Childhood PUV

• Dysplasia
• Prenatal markers
  – echogenic, cystic kidneys; severe oligohydramnios, urine electrolytes?
• Postnatal markers – renal parenchymal size
  – Serum Cr nadir, especially in first yr of life
  – Persistent proteinuria
Serum Nadir Cr during the first year of life (SNC1)

- Retrospective cohort study
- 274 consecutive male infants with confirmed PUV
- Underwent intervention for PUV within 90 days of life
- 15% required RRT

Conclusions

• Congenital anomalies remain the major cause of CKD and ESKD in children.
• Increasing evidence CAKUTs have a genetic basis, although combinations of genetic and environmental insults likely account for most CAKUT
• Radiologic features, laboratory markers of renal dysfunction, and urinary markers help predict ESKD.
• Plenty of work left to do!
A Highly Recommended Reference

Thanks
Question #1

• Which of the following mechanisms can cause CAKUT?
  
  (A) Genes
  (B) Environmental exposures
  (C) Syndromes
  (D) None of the above
  (E) A, B, and C
Answer #1

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  (A) Genes (*HNF1B, PAX2*)
  
  (B) Environmental exposures (*ACEi, maternal DM*)
  
  (C) Syndromes (*BOR, renal coloboma*)
  
  (D) None of the above
  
  (E) A, B, and C
Question #2

• Which of the following best predicts need for renal replacement therapy in boys with PUV?

(A) Echogenic, cystic kidneys with poor corticomedullary differentiation
(B) Serum nadir creatinine of \( \geq 1.0 \text{ mg/dL} \) at one year of life
(C) Oligohydramnios
(D) Prematurity / IUGR
(E) None of the above
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Question #3

• Which of the following CAKUTs can occur in the same patient?

(A) Multicystic dysplastic kidney and UPJ obstruction
(B) Duplex kidney and upper pole ureterocele
(C) Renal dysplasia and high-grade VUR
(D) A, B, and C
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