Review of Dent Disease: Disease mechanisms and treatment strategies

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Dent Patient Day
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Chicago, IL
Wishes us well

• And sad to miss!!

• Dr Lada Beara Lasic
Rare/Orphan Diseases

– The FDA defines an orphan disease as:
  • A condition affecting <200,000 Americans or
  • A disease with greater prevalence but no reasonable expectation that drug development costs are recoverable by U.S. sales

• There are an estimated 6,000 rare diseases
• Approximately 25 million Americans have a rare disease
Challenges for Rare Diseases Research

• Disease often not well characterized or defined
• Rarity means:
  – Recruitment for trials is usually quite difficult
  – Study populations become widely dispersed
  – Few expert centers for diagnosis, management, and research
• Often little high-quality evidence available to guide treatment
RKSC World Sites
Crystal deposition and scarring: the common thread
Goals Round 1

- Establish and expand REGISTRIES
- Collaborate with patient organizations for the rapid dissemination of knowledge
- Stimulate generation of testable hypotheses regarding mechanisms of renal injury in these diseases
- Develop cohorts of well-characterized patients for future clinical studies
- Support small scale clinical studies in these cohorts
- Attract and train investigators to rare diseases research in nephrology
- Fund Pilot studies in these rare diseases
Good news

• Refunded for cycle 2 (July 2014)!!
Dent Disease

- **Small protein leak in urine** 99% (+ in female carriers)
- **Increased calcium in urine** 86-90% (+ in female carriers)
- **Calcifications of the kidney** (40-75%)/kidney stones (25%) 
- **Loss of kidney function** (End stage kidney disease 30-80% by 30-50 y/o)
  - Rickets 25%
  - Low serum phosphate with urinary phosphate wasting (20-25%)
  - Amino acid leak in urine (40-50%)
  - Glucose leak in urine (11-17%)
  - short stature/growth delay
Dent Disease Mutations

• 1. 60% CLCN5
   Dent 1

• 2. 15% OCRL1
   Dent 2

• 3. 25% unknown mutation
Dent disease mutations

• No good correlations between type of mutation and disease manifestation identified

• Wide differences between families and within individuals of the same family (who have the same mutation)

• What influences the difference?
KIDNEY STRUCTURE
GLOMERULAR FILTRATION
Almost all of the proteins filtered in glomeruli are removed from the tubular fluid.

- **CLC-5** and **ocrl** - both involved in the proces.
CLCN5 Mutations

Devuyst et al, KI 2005
1. plasma membrane (PM)
2. clathrin coated vesicles (CCVs)
3. multiple endosomal compartments
4. the trans-Golgi network (TGN)
Ongoing RKSC Dent research

1. Dent Disease Registry
   a. Big Success (n=125)

2. Dent Genetic Testing and Biobank
   b. Another big success (n=100)
     Diagnosis
     Genotype-phenotype

3. Phosphorus protocol

4. Biopsy review

5. Prospective protocol
Dent RKSC Registry: A Snapshot (n=125)

- Patients most often diagnosed in early teens
- Only a minority have kidney stones
- Moderate proteinuria, hypercalciuria, hematuria are more common
- Need high index of suspicion for younger males with CKD/proteinuria
Dent Disease – low eGFR at presentation

![Graph showing the relationship between eGFR (ml/min/1.73M²) and age at first lab test for Dent disease and the general population. The graph indicates a lower eGFR at presentation for Dent disease compared to the general population.]
## Dent biobank

<table>
<thead>
<tr>
<th>Dent Genetic Testing</th>
<th>Families</th>
<th>Affected</th>
<th>Carrier</th>
<th>Negative</th>
<th>Novel mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dent 1 (CLCN5)</strong></td>
<td>54</td>
<td>31</td>
<td>20</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td><strong>Dent 2 (OCRL1)</strong></td>
<td>29</td>
<td>2</td>
<td>0</td>
<td>31</td>
<td>1</td>
</tr>
</tbody>
</table>

- Mayo Summer student Kari Mattison (Iowa State) compiling mutation database and looking at untranslated regions in mutation negative patients
Correlations?

• Why are some people doing so well?
• Why are some people progressing faster?
• Important to collect as much data as possible and look at correlations from our registry
Hypercalciuria (high urine calcium) in Dent disease

- Not fully understood
- At least in part due to \( \uparrow 1,25(\text{OH})_2 \)-vitamin D\(_3\)
Hypercalciuria

- Same mutations can be observed with or without hypercalciuria even in the same family
- Small percentage of patients may have nephrocalcinosis without obvious hypercalciuria
- Could this be a result of
  - Different diet?
  - Other genes?
- Current treatments (thiazides/citrates) are poorly tolerated or unproven
Role of phosphorus and FGF23 on urine calcium levels in Dent

- Patients currently enrolling!
- Recruiting patients older than 18 and GFR > 40 ml/min for testing of blood and 24h urine before and after 2 weeks phosphorus supplementation
- Recruiting patients that are younger or have lower GFR to do one blood and 24h urine measurement (without phosphorus supplementation)
- 7 day food diary before measurements
Dent disease kidney biopsy

Hodgin JB et al, KI 2008
Dent Kidney Biopsy Study

• Approved study protocol to review all available kidney biopsies from patients with Dent Disease, in order to determine if they have any common findings

• Correlate biopsy findings with clinical disease and, when available, type of genetic mutation
Prospective cohort

- Dent 1 (n=50)
- Dent 2 (n=20)
- Lowe Syndrome (n=10)
- Dent female carriers (n=20)

<table>
<thead>
<tr>
<th>Data Elements for Prospective Cohort</th>
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<tbody>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>24 hr Urine</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Enrollment only</td>
</tr>
<tr>
<td>DNA, inflammation panel</td>
</tr>
<tr>
<td>RBP; inflammation panel</td>
</tr>
<tr>
<td>Enrollment and Annually</td>
</tr>
<tr>
<td>Biobank; creatinine, calcium*, phosphorus*, PTH*;</td>
</tr>
<tr>
<td>1,25 vitamin D*</td>
</tr>
<tr>
<td>Biobank; creatinine, calcium, phosphorus, citrate,</td>
</tr>
<tr>
<td>sodium, pH, total protein, RBP*, albumin,</td>
</tr>
<tr>
<td>supersaturation profile*</td>
</tr>
<tr>
<td>Clinical history; Physical exam;</td>
</tr>
<tr>
<td>Height/weight/blood pressure; renal ultrasound*;</td>
</tr>
<tr>
<td>HRQoL; clinical questionnaire (see Appendix)</td>
</tr>
</tbody>
</table>

*Encouraged but Optional
Big Plans for the next 5 years

• What we need from you
  – Participation in research protocols
    • Phosphorous protocol
    • Biopsy protocol
    • Prospective cohort
    • Continue to update registry
Patient questions

• History of Dent(s)
• Doctors of Dent(s)
  – *Charles Dent, Oliver Wrong, Raj Thakker, Steve Scheinman*

• Do mutations differ between individuals in the same family?
• Do mutations change in each generation of a family?
• What role does calcium (Vitamin D) play?
• What role does phosphorus play?
• What role does protein play?
• What role does diet play?
• Why does it affect growth/height?
• What treatments work the best?
• Are there drugs to slow down the loss of protein?
Patient Questions

- Are there drugs to slow down scarring of the kidney tissue?
- What is the consensus around donating a kidney before the patient's kidney stops functioning?
- Why can't the mothers of patients donate their kidney?
- Does everyone one have stones with this disease?
- What is the criteria to be on a kidney transplant list?
- What is the cost involved in a transplant and/or dialysis?
- Do you have to have insurance to qualify for a kidney transplant?
- Can measuring Cystatin C in blood assess kidney function?
- Mediterranean Style Diet, is that good for those with Dent (s)?
- Can the drug Orenzial help reduce the loss of protein for Dent patients?
  - *Abatacept; anti CD 80 antibody on T cells*
- Can the drug CWHM-12 help reduce scarring of the kidney's in Dent patients?
  - Small molecule that blocks $\alpha_v$ integrins
- Do you have to tell your employer about your genetic disease?
Acknowledgements

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RARE KIDNEY STONE CONSORTIUM

RARE DISEASES CLINICAL RESEARCH NETWORK

NYU Langone Medical Center
Treatment of Dent disease

1. Reduce hypercalciuria \(a/w\) kidney stones and nephrocalcinosis
2. Reduce proteinuria
3. Dietary modifications?
   \(1+2+3 = \) Hope to reduce progression of kidney failure
4. Future – targeted molecular therapies?
Reduce hypercalciuria a/w nephrolithiasis and nephrocalcinosis

a. Increased fluid intake – 2.5-3l/day (96 onz)
b. Salt restriction
c. Medications to reduce Ca excretion in the urine: thiazides
d. Citrate
  • (studies in CLC-5-deficient mice suggest long-term control of hypercalciuria by a high citrate diet delays progression of renal disease)
Treatment of Dent disease

- Parents observed children have **increased thirst**. Patients make **larger amount of urine** – possibly defect in urine concentration ability.
- **Increased tendency to “dehydration”?**
- Adverse events associated with “dehydration” – worsening of kidney function (especially when taking other medications like motrin, naprosyn), lightheadedness and fainting
- **Be sensitive to conditions that can cause dehydration. Make sure intake of fluid is increased!**
Treatment of Dent disease

• 2. Proteinuria
• Starts as leak of small proteins with minimal leak of albumin, however patients eventually develop significant leak of albumin
• Renal biopsy findings often shows FGGS or FSGS
• treated with **ACE inhibitors/ARB** (lisinopril, accupril, losartan etc) to delay progression of disease
• What is the role of **ACE inhibitors/ARB** in **DENT**?
Treatment of Dent disease

3. Dietary modifications?
A. What is the role of salt restriction?
B. Protein restriction?
Since disease develops in childhood, what is the time to start, if ever, protein restriction?
C. Potassium restriction?
D. Calcium restriction – NO!
Treatment of Dent disease

• HEALTHY LIFESTYLE
• Diet rich in fruits and vegetables but avoid foods rich in oxalates (rhubarb, beets, okra, spinach, Swiss chard, sweet potatoes, nuts, tea, chocolate and soy products).
• Avoid smoking
• Alcohol in moderation
Treatment of Dent Disease/renal manifestations of Lowe Syndrome

• 4. Future – targeted molecular therapies?
  • How far are we?
  • Need for parallel research in the lab and clinical research
  • Registry is an important step
  • Large role of patient-driven research: patients should be encouraged to participate!