A RARE CAUSE OF FANCONI SYNDROME - DENT’S DISEASE

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History

- 2 years 10 months male child born to consanguineous parents (9.06.2012)
- Birth Wt: 2.8 kg
- Presented elsewhere at 15 months of age with delayed milestones, generalized bony deformities and found to have glycosuria
Contd...

- Diagnosed as Vitamin D deficiency rickets
- Treated outside with Vit.D and Ca supplements for 6 months
- In view of persistent bony deformities child was referred here.
ANTHROPOMETRY

- Height: 76 cm (<10th percentile)
- Weight: 9.5 kg (<10th percentile)
- Head circumference: 46 cm (<50th percentile)
Examination

- Alert
- No edema
- Normotensive
- Genuvalgum
- Widening of wrist
- Dentition normal
- Eyes normal
- Systems normal
## Investigations

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<tr>
<th>Date</th>
<th>S.Cr</th>
<th>Na</th>
<th>K</th>
<th>HCO₃⁻</th>
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<th>Alb</th>
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<th>P</th>
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<td>9.0</td>
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PTH : 71.6 (16.5.14)
RBS : 85
Urine analysis

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<td>Sugar</td>
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<td>Ca/ Cr</td>
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USG abdomen (3.9.13): RK - 6.1 cms, LK - 6.0 cms
Increased cortical echoes
X-ray wrist (2.9.13)- features of rickets
X-Ray Ankles
SUMMARY OF FINDINGS

- Hypocalcemia
- Hypophosphatemia
- Increased alkaline phosphatase
- Metabolic acidosis
- Vitamin D deficiency
- Hypercalciuria
- Glycosuria
- Proteinuria
- Increased PTH
- X-ray features of Rickets
- Increased cortical echoes by USG
Treatment

- Vit D supplementation
- Alkali therapy
- Phosphorus
## After Treatment

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Beta-2-microglobulin >20,000 (670-2143ng/ml)
Discussion

Introduction

- X-linked recessive renal Fanconi syndrome

**Synonyms:**
- Dent disease I
- X-LR hypercalciuric hypophosphataemic rickets
- LMWP with hypercalciuria and nephrocalcinosis
- Dent disease II

- Caused by mutation in CLCN5 gene which encodes the electrogenic chloride / proton exchanger located in chromosome Xp11-22
Disruption or mutations in CIC-5 impairs or alters membrane trafficking via receptor mediated endocytic pathway that involves megalin and cubulin and significantly reduce or eliminate the chloride transport.
Pathophysiology

- Selective urinary loss of LMW proteins in Dent’s indicates that glomerular filter is undamaged and only problem in proximal tubular endocytosis
- CIC-5 protein seems to be critical for acidification of the endosomes that participate in solute reabsorption and membrane recycling in PTC
Contd...
Role of CLC-5

- CLC-5 is a 2Cl⁻/H⁺ exchanger rather than a chloride channel which will facilitate acidification.
PATHOPHYSIOLOGY

Proximal Tubule

LMW Proteins

Urine

Blood

Recycling Endosome

Early Endosome

Lysosome

ATP

ADP+Pi

H^+

2CF

CIC-5

Knock-out

H^+

ATP

CIC-5^-
Acidification of the endosomes results in the dissociation of receptor-ligand complexes. Megalin and Cubilin are then recycled to the apical membrane. The ligand is transported to lysosomes for degradation. Impaired acidification leads to the mutation of ClC-5 ability.
Clinical phenotype

- Dent’s 1 - CLC 5 gene mutation - 60%
- Dent’s 2 - OCRL1 gene mutation 15%
- Males are affected and females have minor phenotype
- Have variable manifestation of proximal tubule dysfunction (partial Fanconi)
- 10% of patients denovo mutation
### Clinical and biochemical characteristics of Dent’s Disease patients with CLCN5 mutation

<table>
<thead>
<tr>
<th>Clinical/biochemical characteristics</th>
<th>Consistency of presence in Dent’s disease patients with mutations in CLCN5(%)</th>
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<tbody>
<tr>
<td>LM WP</td>
<td>100</td>
</tr>
<tr>
<td>Aminoaciduria</td>
<td>44</td>
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<tr>
<td>Glycosuria</td>
<td>19</td>
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<tr>
<td>Hypophosphatemia</td>
<td>32</td>
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<tr>
<td>Hypercalciuria</td>
<td>89</td>
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<tr>
<td>Nephrocalcinosis</td>
<td>76</td>
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<tr>
<td>Nephrolithiasis</td>
<td>41</td>
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<tr>
<td>Renal failure</td>
<td>42</td>
</tr>
<tr>
<td>Rickets/osteomalacia</td>
<td>33</td>
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<tr>
<td>Hematuria</td>
<td>94</td>
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<tr>
<td>Concentrating defect</td>
<td>82</td>
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PTH

Regulates Na coupled phosphate cotransporter (NaPi-IIa)

Uptake of phosphate in PT

PTH not reabsorbed. Accumulates in distal part of PT

Increase PTH in urine

Stimulation of apical PTH receptors in late proximal tubular cells

Internalization & degradation of NaPi-IIa from the membrane

Phosphaturia

PTH is filtered through glomerulus and removed from urine by megalin dependent endocytosis
Urinary loss of vitamin D binding protein leads to bone defects.

Nephrolithiasis:

i) Due to deceased renal function

ii) Impaired handling of Ca phosphate and Ca oxalate crystals in CD
Contd….

- **Glucosuria and aminoaciduria**: failure to recycle their transporters to apical membrane

- **ESRD**: It has been found potentially bioactive hormones PTH, insulin, IG-F in tubular fluid contributes to hypercalciuria and interstitial fibrosis and progressive renal failure.
Diagnosis

- Dent’s Disease is probably under-diagnosed
- Presence of LMWP and at least one of the variable characteristics or a positive family history
- Clinical diagnosis is supported by history of X-linked inheritance of renal Fanconi syndrome
Diagnostic criteria

- Presence of all three of the following criteria:
  - LMWP – increased β2 microglobulin (1 gm/day), Clara cell protein, RBP by at least 5 fold increase
  - Hypercalciuria > 4 mg/kg or Urine Ca/Cr > 0.25 mg/mg
  - One of the following:
    - Nephrocalcinosis
    - Kidney stones
    - Hematuria
    - Hypophosphatemia
    - Renal insufficiency
Treatment

- Supportives - generous fluid intake
- Vit D - indicated only with clinical bone disease
- Phosphate supplements
- Thiazide
- Citrate supplementation
- Genetic counseling
TAKE HOME MESSAGE

- Male Child
- Consanguinity
- Early onset rickets
  - Persistent Hypercalciuria
  - Early biochemical response
  - Parenchymal changes
  - 2 microglobulin