Update on Hypophosphatemic Rickets

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Clarification

- All types of rickets are hypophosphatemic (after all we now know that rickets is *caused* by hypophosphatemia)

- The hypophosphatemia can be due to either:
  - (a) Disturbances in vitamin D/calcium metabolism causing 2\textsuperscript{nd} hyperparathyroidism
  - (b) Insufficient intake/malabsorption or increased renal tubular losses (normal PTH)

- Today we will talk about the most common genetic form: Familial X-linked hypophosphatemic rickets (XLH)
Pathophysiology of XLH

Children – rickets and osteomalacia
Adults - osteomalacia
FGF23 and LVH in XLH (1)

- In CKD high FGF23 levels are associated with LVH, but the cause and effect relationships are yet unknown.

- High FGF23 levels in XLH provide the opportunity to study the heart’s condition without the presence of the many other confounders present in CKD (anemia, hyperparathyroidism, acidosis, etc.).

- A study in the male Hyp mouse (the animal model of XLH) showed no evidence of LVH in spite of high circulating FGF23 level*

Liu ES, Endocrinology 2018;159:2165
FGF23 and LVH in XLH (2)

- A few studies were done on XLH patients, and showed that besides a few, most patients do not have echocardiographic abnormalities*

- One has to remember though that whereas in CKD FGF23 levels are in the thousands, in XLH they are in the low hundreds

- Thus XLH may not be the optimal model to learn the effect of FGF23 on the heart

* Vered I, JBMR 1990;5:469 – 0/11
• Hernandez-Frias O, Pediatr Nephrol 2019: Jan – 4/23 LVH, w/o correlation with FGF23
XLH: Principles of Traditional Treatment (1)

- Traditional treatment of XLH is based on the **combination** of high doses of oral phosphate and calcitriol with the goal to raise serum P*
- Phosphate is given to compensate for its tubular losses (in essence we are chasing our tail)
- Calcitriol is given for two reasons:
  (a) To enhance phosphate absorption from the gut
  (b) To suppress the parathyroid glands, as they are repeatedly stimulated by the frequent administration of phosphate (3-4 times/day) that each time lowers serum Ca++ concentration

* At times it is OK to give calcitriol alone, but **never** P alone
XLH: Acute Effect of Oral Phosphate Administration on Serum Phosphate, Ca^{++} and PTH (blue line)

1. 8 children with XLH, off medications
2. Received a single oral P dose on Day 1
3. Blood samples obtained every 30 min

The combination of P + calcitriol is quite effective in healing the rickets, and if started early can also improve growth and avoid the need for orthopedic surgeries.

However it carries high risk of toxicity:

(a) High calcitriol dose can cause hypercalciuria and nephrocalcinosis
(b) High phosphate dose can too cause nephrocalcinosis and 2nd hyperparathyroidism

The hyperparathyroidism insults the kidneys by stimulating calcifications which may result in irreversible kidney damage. Furthermore, hyperparathyroidism further lowers the TP/GFR.

Finally and paradoxically, both P and calcitriol stimulate FGF23 production.
XLH: Traditional treatment requires complex and delicate navigation between curative and toxic doses of medications; namely frequent monitoring of blood and urine biochemical variables and dose adjustments

<table>
<thead>
<tr>
<th>Biochemical Status</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>1. Hypophosphatemia with normal PTH</td>
<td>↑phosphate ↑calcitriol</td>
</tr>
<tr>
<td>2. Hypercalciuria, normal serum calcium</td>
<td>↓calcitriol, and/or ↑phosphate, and/or add thiazide/amiloride</td>
</tr>
<tr>
<td>3. Hypercalcemia with suppressed PTH</td>
<td>Discontinue all medications until serum Ca normalized</td>
</tr>
<tr>
<td>4. Secondary hyperparathyroidism with normocalcemia</td>
<td>↑calcitriol, and/or ↓phosphate; consider Cinacalcet</td>
</tr>
<tr>
<td>5. Secondary hyperparathyroidism with hypercalcemia</td>
<td>Discontinue all medications; consider Cinacalcet</td>
</tr>
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Note the serum alkaline phosphatase activity *per se* is not a factor in treatment adjustment.
XLH: Principles of Treatment (3)

- If PTH is high: lower/stop P dose and increase calcitriol

- In patients who develop resistant hyperparathyroidism, add cinacalcet

- Suppression of the parathyroid glands, besides its protective effect on the kidney, will also elevate TP/GFR enabling the use of lower doses of P and calcitriol.
Acute Effect of Oral Phosphate + Cinacalcet on Serum Phosphate, Ca^{++} and PTH (purple line)

1. 8 children with XLH, off medications
2. Received a single oral P dose on Day 1
3. On Day 2, same P dose + Cinacalcet
4. Blood samples obtained every 30 min

Effect of **Adding** Cinacalcet to XLH Treatment: Results in 6 Patients (expressed as mean±SD)

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 365</th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calciotrol dose</strong> (ng/kg)</td>
<td>16.2±3.5</td>
<td>8.1±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>K-Phos dose</strong> (mg/kg)</td>
<td>31.0±22.9</td>
<td>18.8±17.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>PTH</strong> (pg/ml)</td>
<td>44.4±20.6</td>
<td>15.6±12.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Ca</strong> (mg/dl)</td>
<td>9.82±0.48</td>
<td>8.60±0.40</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>PO₄</strong> (mg/dl)</td>
<td>2.90±0.28</td>
<td>2.74±0.34</td>
<td>NS</td>
</tr>
<tr>
<td><strong>AlK. Phos.</strong> (u/l)</td>
<td>237±145</td>
<td>220±135</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Serum Cr and albumin were normal throughout.
Cinacalcet replacing oral phosphate in a 8y old boy with XLH

Nine months of treatment with Cinacalcet

A = before - rickets
B = after - healed

Alon US, Clinical Endocrinol 2017;87:114
Cinacalcet in XLH

- If used, it is important to watch:
  (a) serum ionized Ca which may drop and require more calcitriol
  (b) urine Ca which may rise (due to stimulation of the CaSR in the loop of Henle) requiring the addition of thiazide/amiloride

- Cinacalcet is nevertheless the current best option in those who developed secondary or tertiary hyperparathyroidism, before surgical parathyroidectomy becomes inevitable
Treatment of XLH: The Future is here

- Agents to block the effect of FGF23 on its target organ (proximal tubule cell)
- Enzymes to cleave FGF23
- Antibodies to FGF23
Effect of Anti-FGF23 Neutralizing Antibodies on the Hyp Mouse: Serum Phosphate and 1,25(OH)$_2$D

Aono Y, JBMR 26:803, 2011
Effect of Anti-FGF23 Neutralizing Antibodies on the Hyp Mouse: Histomorphology

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<tr>
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<th>Hyp</th>
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<tbody>
<tr>
<td></td>
<td>Control Ab (16)</td>
<td>FGF23 Ab (4)</td>
</tr>
<tr>
<td></td>
<td>Control Ab (16)</td>
<td>FGF23 Ab (16)</td>
</tr>
</tbody>
</table>

Aono Y, JBMR 26:803, 2011

Red – unmineralized osteoid
Green – mineralized bone
Burosumab in action – reversing the effects of too high FGF23 levels

Emma F, KI 2018;94:846
Burosemab (Crysvita)

- A fully human anti FGF-23 IgG1 antibody
- FDA approved in April 2018 (now approved also in Europe for children)
- Subcutaneous injection (by a health professional)
  - q 2 weeks in children (1-18y)
  - q 4 weeks in adults
- Results in sustained normalization of serum phosphate concentration and decrease in alkaline phosphatase
- Serum Ca, PTH, Cr and urine Ca/Cr stay normal
- Improvement in bone condition* and growth

*By X-rays in children, and histomorphology in adults
Effect of Burosumab (vs. placebo) on serum phosphate in adults with XLH
Effect of Burosumab (vs. placebo) on serum and urine calcium and plasma PTH in adults with XLH

Insogna K., JBMR 2018;33:1383
Effect of Burosumab on children with XLH (1)

Carpenter T, NEJM Ed 2018;378:1987
Whyte M, The Lancet 2019;January 9
Effect of Burosumab on children with XLH (2)

Rickets healed/improved; growth Z-score improved by 0.19
In summary

- XLH may not be the best model to assess the effect of FGF23 on the heart.

- The recent breakthrough in XLH management is the availability of anti-FGF23 antibodies (Burosumab); it simplifies treatment and does not have the adverse effects seen with traditional treatment.

- In patients who cannot receive Burosumab, consider adding cinacalcet and lowering/eliminating phosphate (do not forget that treatment with a calcimimetic agent will often require an increase in the dose of calcitriol and the addition of thiazide diuretics).