X-linked Hypophosphataemic Rickets

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What is rickets?

• Failure to mineralise newly-formed bone
• Increase in growth plate hypertrophic chondrocyte cell layer
Bones – general structure

- Cortex
- Trabeculae
- Growth plate
- Modelling
- Remodelling
Rachitic mouse growth plates

Tissue Mineralisation

Osteoblast Cytosol

Extracellular

ADP
ATP

PP_i
PP_i
PP_i
PP_i

Enzyme: ENPP1

Ankylase: ANK

TNSALP

Matrix Vesicle

Ca
P_i
P_i

Phosphatase: PHOSPHO1

Enzyme: ENPP1

PEA
PChol

ADP
ATP

Ca^{++}

Phosphate

Phosphate intake from food 32 mmol 

Formation 8 mmol 

Reabsorption 8 mmol 

Net intestinal absorption 21 mmol 

Fecal excretion 11 mmol 

Bone 

Extracellular fluid phosphorus 22 mmol 

208 mmol 187 mmol 

Phosphorus excreted in urine 21 mmol 

Naderi A. doi:10.1038/nrneph.2010.121
1,25(OH)$_2$D$_3$

Low Pi diet

- Pi
- 3 Na$^+$
- NPT2b

Active (transcellular)

High Pi diet

Passive (paracelllular)

VDR

Christakos S et al. doi:10.1038/bonekey.2013.230
Phosphate excretion

- 60-70% reabsorption in PCT
- NaPi2a and NaPi2c
- PTH
- FGF23
- NHERF-1
- FGFR1, 3 and 4
XLH – history

• 1937 Albright – VDRR
• 1940 Christensen – familial
• 1958 Winters – X-linked dominant
• 1976 Eicher – HYP mouse
• 1985 Harrell – use of calcitriol to heal osteomalacia
• 1986 Read – short arm X chromosome
• 1987 Thakker – Xp22
• 1995 Francis – P(H)EX
• 2000 Econ – FGF23 in ADHR
XLH - diagnosis

- Clinical
- Imaging
- Biochemical
- Genetic
XLH – clinical manifestations 1

- Long bones
  - Rickets
  - Deformity
  - Short stature

- Slight delay puberty
  - PHV 13 and 15 yrs girls and boys, respectively
XLH – clinical manifestation 2

• Skull
  • Craniosynostosis (75%)
  • Chiari type 1 (48% tonsillar herniation)
  • Syringomyelia (>16%)

• Teeth
  • Abscess – 61.5% adults with Hx 5 or more cf 5% with 1 in general population
  • Periodontitis

• Myopathy
• Enthesopathy
• Osteoarthropathy
XLH – history of treatment

• High dose vitamin D (1937)
  • Toxicity risk
• Phosphate and vitamin D (1972)
  • Growth plate effect
• Phosphate and activated vitamin D (1980)
• Activated vitamin D alone?
XLH – “traditional” medical management

• General approach
  • Phosphate
  • Activated form of vitamin D
• Monitoring for side-effects
• Other effects of treatment
  • PTH
  • FGF23
XLH – current surgical management

- Guided growth
- Osteotomy
- Cranial surgery
FGF23 in bone

Sapir-Koren R. DOI: 10.1002/biof.1186
FGF23

• Hormone produced by osteoblasts and osteocytes
• Regulated by:
  • 1,25 OH₂ vitamin D
  • PTH
  • PHEX (local)
  • Mineralisation
ARHR

Feng JQ et al. Nature Genetics 2006;38:1310-5
DMP1-/- osteocytes

Feng JQ et al. Nature Genetics 2006;38:1310-5
PHEX and DMP1 - ASARM

ASARM = Acidic Serine Aspartate-Rich MEPE

ASARM: peptide or motif
May compete for binding to PHEX

Rowe P. DOI: 10.1002/cbf.2841
Burosumab Therapy in Children with X-Linked Hypophosphatemia

Thomas O. Carpenter, M.D., Michael P. Whyte, M.D., Erik A. Imel, M.D.,
Annemieke M. Boot, M.D., Ph.D., Wolfgang Högler, M.D.,
Agnès Linglart, M.D., Ph.D., Raja Padidela, M.D., William van’t Hoff, M.D.,
Meng Mao, Ph.D., Chao-Yin Chen, Ph.D., Alison Skrinar, Ph.D.,
Emil Kakkis, M.D., Ph.D., Javier San Martin, M.D., and Anthony A. Portale, M.D.
Change in rickets severity with burosomab

Exemplar radiographic change

Improved serum phosphorus

Reduced serum Alkaline Phosphatase

Effect on growth and walking

Standing Height Z Score for All Subjects

- Every 2-Weeks (n = 26)
- Every 4-Weeks (n = 26)

6-Minute Walk Test in Subjects with Impairment at Baseline (<80% Percentage of Predicted)

- Every 2-Weeks (n = 14)
- Every 4-Weeks (n = 10)

# Adverse events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Burosumab Every 2 Weeks (N = 26)</th>
<th>Burosumab Every 4 Weeks (N = 26)</th>
<th>All Patients (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>26 (100)</td>
<td>26 (100)</td>
<td>52 (100)</td>
</tr>
<tr>
<td>Adverse events with ≥15% incidence in both groups combined</td>
<td></td>
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</tr>
<tr>
<td>Injection-site reaction*</td>
<td>17 (65.4)</td>
<td>13 (50.0)</td>
<td>30 (57.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (61.5)</td>
<td>10 (38.5)</td>
<td>26 (50.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>15 (57.7)</td>
<td>8 (30.8)</td>
<td>23 (44.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (30.8)</td>
<td>13 (50.0)</td>
<td>21 (40.4)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>9 (34.6)</td>
<td>12 (46.2)</td>
<td>21 (40.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9 (34.6)</td>
<td>9 (34.6)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (38.5)</td>
<td>8 (30.8)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (26.9)</td>
<td>10 (38.5)</td>
<td>17 (32.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (30.8)</td>
<td>8 (30.8)</td>
<td>16 (30.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (26.9)</td>
<td>6 (23.1)</td>
<td>13 (25.0)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>5 (19.2)</td>
<td>8 (30.8)</td>
<td>13 (25.0)</td>
</tr>
</tbody>
</table>
Summary

• XLH is caused by mutations in PHEX
• Increased FGF23 activity results in rickets
• Burosumab is an effective treatment for XLH
Thank you – questions?