Rickets: Case Presentation
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• CC: lower extremity angular deformities and growth failure

• HPI:
  – 16 year old male, referred to bone clinic from orthopedics prior to corrective osteotomies
  – Bilateral leg deformities—genu valgum of unclear duration. Noted to be severe and progressing by the family for the past two years
  – Short stature “always”—treated with GH for two years without growth benefit and with worsening deformities

• PMH/Development:
  – Mild learning disability, otherwise healthy
• **FHx:**
  – Sister with congenital metatarsus adductus, otherwise no similar boney abnormalities, fractures, or osteoporosis

• **No Meds**

• **ROS negative other than HPI**

• **PE:**
  – Ht: <5%, Wt: 75%
  – Normal blood pressure
  – Bilateral, severe genu valgum, right>left
  – Normal reflexes and muscle tone
  – No dysmorphic features
  – No rashes, café-au-lait spots, birthmarks, or sacral dimples
• Imaging
  – Bone age X-ray bone age approximates 14 years (delayed from chronologic age of 16 years)

• Labs:
  – Na141/K 3.5/Cl 107/ CO2 21/ BUN 10/ crea 0.7/ Ca 9.2/ Phos 2.6/ Alk Phos 419
  – TSH - 1.67
  – intact PTH 60
  – 25-OH vitamin D – 17
  – 1,25 OH vitamin D – 29
  – Urine Ca/crea ratio - 0.06
  – Fractional Excretion of Phosphorus - 11% (Normal 10-15%)
  – Calculated TmP/GFR [Maximal Tubular Phosphate Reabsorption] - 2.3 (Normal 2.8 - 4.4 mg/dl)
Rickets

• Deformities and Poor Growth

• Abnormal mineralization of bone
  – Insufficient substrate:
    • Nutritional deficiency of phosphorus, vitamin D
    • Excess phosphate wasting due to FGF-23
      – ADHR, TIO, XLH
  – Alterations in the mineral process
    • Renal failure
    • Hypophosphatasia
    • Genetic syndromes with local alterations in bone
Rickets: Phenotype
Rickets: Workup

- X-rays
- Calcium, Phosphorus levels
- PTH
- Alkaline phosphatase
- Vitamin D
  - 25(OH)
  - 1,25dihydroxy
- Genetics
- FGF-23
Skeletal Mineralization
New Markers of Mineralization

Human disease states:
ADHR, XLH
ESRD
FGF-23 Regulation

Osteoblast

Osteocyte

↓PHEX

↑DMP-1

↓PHEX

↑1,25(OH)₂D

↑Pi

↑MEPE-ASARM

Dietary animals + humans + CKD

Pituitary
Choroid

DCT → PCT

Klotho

FGF-23

Pituitary Choroid
FGF Knockout: Impaired Skeletal Mineralization

Bone Formation Rate

Log(1st PTH-IMA) vs. BFR(um²/mm³/d)

Log(Intact FGF-23) vs. BFR(um²/mm³/d)

r=0.45, p<0.01

NS
Osteoid Thickness

\[ \log(\text{Intact FGF-23}) \]

\[ \log(1^{\text{st}} \text{PTH-IMA}) \]

\[ r = -0.46, p < 0.05 \]

\[ r = 0.38, p < 0.05 \]
Osteoid Maturation Time

$r=-0.42, p<0.01$

Log(Intact FGF-23) vs. OMT (d)

Log(1st PTH-IMA) vs. OMT (d)
Serum FGF-23 Correlates with Expression in Bone

FGF-23 expression in Human bone samples

\[ r = 0.54, \ p < 0.01 \]
Bone-Kidney-Parathyroid Feedback Loop

- 1,25(OH)$_2$D synthesis
- Klotho
- FGFR
- Vit D
- serum PTH
- Ca$^{2+}$
- FGF23
- phosphaturia
- 1,25(OH)$_2$D synthesis
- phosphaturia
- Ben-Dov, IZ, et al. ASN & JCI 2007:117;4003
Questions

• Defective mineralization: What is the mechanism?

• How do we treat it?