3 month old female with elevated serum alkaline phosphatase

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March 27, 2014
History of Present Illness

• 3 month old female presented after being referred to us for high alkaline phosphatase level.
• She has no history of fractures, seizures, limb deformities and has regular follow-up with her pediatrician.
• She consumes 5 oz formula q 3 hours and has no problems with feeding.
History

• Birth History
  – Born at 38 weeks of gestation via C-section
  – Normal pregnancy
  – Birth weight: 7.5 lbs (50th %ile).
  – Birth length: 20 inches (85th %ile).
  – No post natal complications

• No past medical history
• No past surgical history
• No current medications

• Social history: Lives at home with both parents, mother born in Mexico
Review of Systems

- Constitutional: No change in activity, appetite or diet
- HENT: Negative
- Eyes: Negative
- Respiratory: No respiratory difficulties
- Cardiovascular: No fatigability with feeds
- Gastrointestinal: No vomiting, diarrhea or constipation.
- Genitourinary: 4-5 wet diapers/day
- Musculoskeletal: No history of fractures
- Skin: No rash
- Neurological: Negative
- Hematological: Negative.
Physical Exam

- Vitals normal. Length: 52.96%ile. Weight: 40.75 %ile
- Constitutional: Active, well appearing and well nourished.
- HENT: AF OF
- Nose: No nasal discharge.
- Mouth/Throat: Mucous membranes are moist. Oropharynx is clear.
- Eyes: Normal conjunctivae, red reflex present, normal sclerae
- Neck: Neck supple. No thyromegaly
- Cardiovascular: Normal rate and regular rhythm. Palpable pulses, no murmurs heard.
- Pulmonary/Chest: Normal effort, normal breath sounds . No respiratory distress.
- Abdominal: Soft., No hepatosplenomegaly.
- Genitourinary: Normal female genitalia
- Musculoskeletal: Normal range of motion. No deformities. No joint swelling or leg length discrepancy
- Neurological: Alert and normal muscle tone.
- Skin: Nevus flamus on posterior neck. Slate gray macule on caput. No cyanosis. No pallor.
Initial laboratory evaluation

- Na: 139 meQ/L
- K: 5.5 meQ/L
- Cl: 107 meQ/L
- CO2: 20 meQ/L
- BUN: 9 mg/dL
- Cr: 0.3 mg/dL
- Ca: 9.7 mg/dL (11 days - 1 year: 9.2 - 11.0 mg/dL)
- iPhos: 2.8 mg/dL (10 d-24 mo: 4-6.5 mg/dL)
- Mg: 2.2 mg/dL (1.6-2.5 mg/dL)
- Alk Phos: 982 U/L (infants 150-420 U/L)
- 25-OH vit D 26 (30-100)
- Urine Phos: 34.2 mg/dL
- Urine Ca: 1.5 mg/dL
- Urine Cr: 15 mg/dL
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DIFFERENTIAL DIAGNOSIS?
Differential Diagnosis

• Vitamin D Deficiency
• Hypophosphatemic Rickets
  – X-linked hypophosphatemic rickets
  – Autosomal dominant hypophosphatemic rickets
  – Autosomal recessive hypophosphatemic rickets
  – Hypophosphatemic rickets with hypercalciuria
• Acquired renal phosphate wasting
  – Fanconi Syndrome
  – Tumor induced osteomalacia
• Primary Hyperparathyroidism
Family History

• Mother diagnosed at 5y, had severe bowing requiring osteotomy. Treated with Ca, P, calcitriol until 23 y. Resumed therapy at 28 y during pregnancy. + Poor dentition, denies fractures, bone pain, arthritis, nephrocalcinosis. No siblings

• Maternal Grandmother diagnosed during teen years, short stature, bowing, + arthritis. No siblings

• Hts: Mother: 4’9”. Father: 6’2”
Patient course

• Genetic consult
• Revealed a partial deletion of PHEX gene confirming X-linked hypophosphatemic rickets
X-linked hypophosphatemic Rickets (XLH)

- Prevalence of 1 in 20,000
  - 80% of cases of familial phosphate wasting
- No predominance in either sex
  - No evidence of gene dosage effect, imprinting or genetic anticipation
- Mutation in the PHEX gene on Xp22.1
  - Not expressed in kidney
  - Codes for cell surface-bound protein cleaving enzyme
Pathogenesis of XLH

Pathways of renal phosphate wasting in hereditary hypophosphatemic rickets and tumor-induced osteomalacia

Levels of FGF-23 are increased by inactivating mutations in PHEX (as in XLH) or DMP1 (as in ARHR), by activating mutations in FGF-23 (as in ADHR), or by tumor production of FGF-23 (as in TIO). Each of these disorders leads to excessive activity of FGF-23, which suppresses the Na/Pi cotransporter and causes renal phosphate wasting. In HHRH the renal phosphate wasting is caused by a mutation in the Na/Pi cotransporter itself.

XLH: X-linked hypophosphatemic rickets.
ADHR: Autosomal dominant hypophosphatemic rickets.
ARHR: Autosomal recessive hypophosphatemic rickets.
TIO: Tumor-induced osteomalacia.
HHRH: Hereditary hypophosphatemic rickets with hypercalcuria.
PHEX: Phosphate regulating endopeptidase on the X chromosome.
DMP1: Dentin matrix protein 1.
FGF-23: Fibroblast growth factor 23.
Recommended Medical Therapy

• Combined treatment with oral phosphate and calcitriol.
  – Recommended dose of calcitriol: 20 to 30 ng/kg/day in 2-3 divided doses*
  – Recommended elemental phosphorus dose: 20-40 mg/kg/day (in 3-5 divided doses)*

Goals of treatment

- To correct or minimize rickets/osteomalacia, radiographic abnormalities, and skeletal deformities.
- **NOT** to normalize serum phosphate concentration
  - Common misconception
  - Likely to do harm
- Maintenance of acceptable height velocity and improvement in skeletal deformities indicate satisfactory dosing.
- Serum alkaline phosphatase activity is the most useful surrogate biomarker for bone healing
  - Moderately elevated before Rx, then decreases with Rx
  - Transient increase when Rx is initiated.

CLINICAL QUESTIONS

• What are the pitfalls of combined therapy with oral phosphate and calcitriol?

• What adjunctive therapies are possible and what are their outcomes?
COMPLICATIONS OF THERAPY WITH ORAL PHOS AND CALCITRIOL

• Hyperparathyroidism
  – Overtreatment with Phos or undertreatment with Calcitriol
  – Corrected by increasing the calcitriol dose and/or by reducing the phosphate dose
  – Monitor epiphyseal healing, serum and urine calcium

• Nephrocalcinosis
  – Treatment with Phos corrects serum levels by increasing phosphate absorption from the gastrointestinal tract
  – Monitor with renal US every 2-5 years
  – Mild nephrocalcinosis: no significant clinical sequelae
  – Radiography and CT are not recommended

ADJUNCTIVE THERAPIES

• Hydrochlorothiazide
  – Decreases urinary calcium excretion
  – Prevents progression of nephrocalcinosis in children with XLH

• Growth Hormone
  – Increases linear growth, but disproportionately.
  – GH and IGF-I transiently stimulate phosphate reabsorption, long-term responses have been variable.
  – Based on evidence, benefits don’t outweigh risks.

• Calcimimetics
  – Have been used effectively to reduce PTH in CKD and in tumor-induced osteomalacia.
  – Long-term studies in children with XLH are necessary

Seikaly MG, Baum M. Thiazide diuretics arrest the progression of nephrocalcinosis in children with XLH. Pediatrics 2001; 108:E6
Calcimimetics: Rationale for use

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Calcimimetics

• Modulate the Ca Receptors in parathyroid chief cells.
• Enhances its sensitivity to circulating serum calcium concentrations and decreases PTH secretion
Effect of P loading alone (day 1) compared with P + cinacalcet (day 2) on serum (A) ionized calcium, (B) PTH, and (C) phosphate, in 8 subjects with XLH. Blood samples were obtained every 30 minutes. Data are shown using Random Intercept Mixed Linear Model. The change in ionized calcium was $-0.011$ during the first day and $-0.033$ mmol/L per hour during the second day ($P = 0.0001$, 95% CI $-0.032$ to $-0.014$). The change in PTH was 4.1 during the first day and $-1.9$ pg/ml per hour on the second day ($P = 0.001$, 95% CI $-9.6$ to $-2.5$).
Back to our patient

• She was started on Calcitriol 30 ng/kg/d and Sodium Phosphate 40 mg/kg/day
• Labs 3 days after initiation of therapy: Ca 9 (8.5-10.1)
  – Phos 3 (2.5-4.9)
  – Alk Phos 1136 (54-389)
  – 25-OH vit D 25 (30-100)
  – 1,25-OH Vit D 117 (24-86)
• Most recent dosages: Calcitriol 50 ng/kg/d and sodium Phos 75 mg/kg/day
References

• Seikaly MG, Baum M. Thiazide diuretics arrest the progression of nephrocalcinosis in children with XLH. Pediatrics.2001; 108:E6