

Meet-the-Professor Session: ASBMR 2022: 1:45-2:45 PM, Friday, September 9

Title: Pediatric Metabolic Bone Disease: Challenging Cases in XLH and Other Disorders

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Significance of the Topic:

The increased awareness of metabolic bone diseases in children has resulted in an increase in referrals and diagnostic challenges for the specialty clinician. There is an increased utilization of newer genetic testing platforms and newly accessible biochemical assays which can sometimes be confusing or unexpected. Moreover with newly available therapies, an experience in management with newer agents is emerging. We will discuss 2-3 cases of pediatric metabolic bone disease that will be designed to instruct the natural history, use of newer diagnostic testing, and the course and impact of newer therapies, with a focus on X-Linked Hypophosphatemia.

Learning Objectives

- Understand the natural history and biochemical profile of the disorder.
- Be aware of the increasing number of identified variants that are pathogenic or likely pathogenic for XLH.
- Understand how to interpret laboratory testing as relates to newer modalities in light of physiology
- Be aware of the course of treated disease, both with older and newer therapeutic approaches.
- Remember that not all rickets is XLH.

Points of Interest/Clinical Pearls

- XLH is a multisystem disorder that extends well beyond childhood.
- XLH in adults can be a progressively debilitating disease with severe consequences. (Frequent problems in the adult population include osteoarthritis, enthesopathy, osteophytes, spinal stenosis, loss of hearing, poor dentition.)
- ALWAYS REMEMBER YOU HAVE TO THINK ABOUT ORDERING A SERUM PHOSPHATE.
- IF A PHENOTYPE DOESN'T ALIGN WITH GENETICS, ASK WHY
- "Variant of uncertain significance" is not a fixed description, but may change as further cases are identified.
- Interpret FGF23 levels in relation to the serum phosphate level.
- All rickets is not XLH or vitamin D deficiency, and maybe not even rickets.

Cases

Case 1: A 24 year-old woman with bone pain, chronic mental fog, weakness, and fatigue

This 24 year-old female with a long history of chronic disease, presents with multiple complaints including bone pain and pain with walking. She has never fractured, but has always been short. She had sufficient bow defect to require epiphysiodesis at age 11-12; no biochemical investigation for bowing was performed. She went on to require surgical decompression for Chiari 1 malformation 3 yrs ago and believes her condition deteriorated following this surgery at age. This was a partial decompression and C1 laminectomy.

She is affected with depression, anxiety and features consistent with chronic fatigue. Concomitant headache, dizziness, "foggy brain," decreased hearing, and jaw pain prompted MRI studies; mild disk herniations at C4-5, C5-6, T7-8, L5, and S1 were identified. Subsequent imaging revealed osteophytes at L1-2, L2-3, L3-4, L4-5, L5-S1, and C4-5 as well as arthropathy of the facet joints at C7-T1, C6-C7, and T7-T8.

Her overall course has been declining, and she no longer lives independently. The only available biochemical investigations were done in 2019 (serum calcium = 8.7 mg/dL, alkaline phosphatase = 77 IU/L, serum phosphorus = 2.2 mg/dL).

Review of Systems: She complains of spontaneous muscle "tension" and frequent lower back and neck pain. She has experienced bladder incontinence and has been told it is likely related to the Chiari correction surgery. Difficulty swallowing, and occasional emesis occur. No dental abscesses.

Medications:

Vyvanse, Effexor (SSRI)

PRN: Colace, Aleve, Allegra, Flonase, Albuterol
symbicort

Family History: No known family history of XLH.

After online searching, she considered that she may in fact be affected with X-linked hypophosphatemia and she thus sought assistance of a private practice geneticist.

PHYSICAL EXAM:

Height 4' 10.7" (1.491 m)

Weight 48.4 kg

Short with no other overt dysmorphic features. Dentition is with no obvious dental abscesses); hoarse voice. Neck with limited range of motion; patellar reflexes 3+. No pain with spine percussion. Right anterior tibia is painful to deep palpation. Gait reveals intoeing on right side during ambulation. Intolerant of tiptoe walking due to discomfort. No leg bowing.

PHEX analysis revealed a "variant of uncertain significance": *PHEX* c.1328G>A p.R443H. Neither parent had any abnormality in *PHEX*.

Biochemical evaluation at our center revealed:

		Reference Range
Creatinine	0.64	0.40 - 1.30 mg/dL
Calcium	8.9	8.8 - 10.2 mg/dL
Phosphorus	1.8	2.2 - 4.5 mg/dL
Alkaline Phosphatase	71	9 - 122 U/L
Alkaline Phosphatase, Bone Specific	13.5	4.7 - 17.8 mcg/L
Parathyroid Hormone, Intact	67.9	15.0 - 65.0 pg/mL
Vitamin D, 1,25-Dihydroxy	49	25 - 66 pg/mL
Vitamin D25-Hydroxy	20	20 - 50 ng/mL
Creatinine, Urine, Random	54	
pH, UA	8.5	5.5 - 7.5
Calcium, Urine, Random	3.3	
Phosphorus, Urine, Random	28.3	
INTACT FIBROBLAST GROWTH FACTOR 23	29	

TRP = 81% TMP/GFR = 1.45 mg/dl

Questions:

Does this woman have XLH? If not, what other diagnoses are likely?

How should a “variant of uncertain significance” be interpreted upon genetic testing?

How should FGF23 level be interpreted?

What is the cause of the arthropathy and osteophytes?

How would you proceed with management?

Case 2: A damaging mutation in PHEX, but not XLH

A 10-month-old girl was referred for treatment and management for presumed XLH. Prenatal ultrasonography identified duodenal atresia, polyhydramnios and intrauterine growth restriction. An amniocentesis was therefore performed, revealing an X-chromosomal deletion, (extending from Xp22.12→Xp22.11), and encompassing 10 genes including *PHEX* (2 of which are associated with X-linked recessive disorders).

She was born at 37.5 weeks gestation and underwent repair of the duodenal atresia without complications. A repeat analysis on a DNA sample from the child confirmed that the infant carried the deletion noted above. However, she exhibited normal linear growth (along 47th-64th centiles), met all age-appropriate developmental milestones, and demonstrated no phenotypic features of XLH. Serial radiographic assessments were normal. Neither parent had features of XLH, nor carried the deletion.

Serial laboratory values were as follows:

	2 days	1 wk	2 wks	3 wks	4 mos	5 mos	8 mos
Calcium	10.3	10.9	10.3	10.2	11.2	10.3	10.5
Albumin	3.6	3.4	2.7	3.0	4.4	4.0	4.6
Alkaline Phosphatase	90	134	135	186	203	246	238
Phosphorus	5.3	6.2	6.4	6.1	7.4	6.5	5.9
Vitamin D 1,25					145	67	114
Vitamin D,25					182.8	70.8	39.5
Intact PTH					6.4	22	15
FGF-23						223	279

Questions:

Does this child have XLH?

How would you treat her?

How should FGF23 level be interpreted?

How can the absence of phenotypic and biochemical features of XLH be explained with a documented de novo deletion of *PHEX*?

Case 3: Rickets on X-ray, but no biochemical findings

An 8-month-old child was referred because of abnormal radiographs suggestive of rickets. Bilateral clubfoot deformity was noticed at birth and managed with casting and Achilles tenotomy. In the course of routine orthopedic follow-up, he was noted to have asymmetric skin folds around his mid-calf areas, and the lower extremities were imaged radiographically, revealing frayed and widened metaphyses, typical of rickets.

After an uneventful pregnancy, he was born at term and solely breastfed for 3 months, when formula was introduced. A combination of breast milk and formula were provided from 3 - 5 months of age. At 5 months, breast milk was discontinued and he was strictly formula fed, with solid foods gradually introduced shortly thereafter. He was administered supplemental vitamin

D during the 1st 3 months of life when breastfeeding, and discontinued when starting the formula.

Otherwise, he has been healthy without any problems.

He has met all milestones on time and is now getting his 1st teeth erupting.

FAMILY HISTORY:

Negative for any kind of familial rickets, osteoporosis or bone disease. Of interest, the paternal grandfather also had clubfeet and wore leg braces early in childhood which he subsequently discontinued. He grew to a height of 5 feet 10 inches. The father is 6' 2" and mother is 4' 11" .

PHYSICAL EXAM:

Weight: 8.29 kg (32 %, Z= -0.48)

Height: 2' 2" (0.66 m) (1 %, Z= -2.31)

Mild midfacial flattening and a slightly tall head. There is generous adipose tissue in his lower extremities, a mild bow is evident, but difficult to separate from physiologic bowing.

LABS:

		Ref. Range
Calcium, Ionized, Serum	5.80	4.65 - 5.28 mg/dL
Phosphorus	5.3	3.0 - 7.0 mg/dL
Alkaline Phosphatase	243	80 - 380 U/L
Parathyroid Hormone, Intact	22.3	15.0 - 65.0 pg/mL
25-Hydroxy Vitamin D	47	

EXTENDED RADIOGRAPHIC SURVEY: Similar fraying changes seen in proximal humerus, distal radius, as well as distal femur and proximal tibia. The spine films revealed no abnormalities.

Questions:

Does this child have rickets?

What is the differential diagnosis?

What further tests would be useful?

How can the absence of biochemical features of rickets be explained with overt radiographic findings?

Genetics: One "variant of uncertain significance" and one pathogenic variant observed in *MMP13*.

References

Javaid MK, Ward L, et al. [Musculoskeletal features in adults with X-linked hypophosphatemia: an analysis of clinical trial and survey data](#). *J Clin Endocrinol Metab*. 2022 Feb 17;107(3):e1249-e1262. doi: 10.1210/clinem/dgab739. PMID: 34636401

Kato H, Koga M, et al. [Incidence of complications in 25 adult patients with X-linked hypophosphatemia](#). *J Clin Endocrinol Metab*. 2021 Aug 18;106(9):e3682-e3692. doi: 10.1210/clinem/dgab282. PMID: 33912912

Schindeler A, Biggin A, Munns CF. [Clinical evidence for the benefits of burosumab therapy for X-linked hypophosphatemia \(XLH\) and other conditions in adults and children](#). *Front Endocrinol (Lausanne)*. 2020 May 28;11:338. doi: 10.3389/fendo.2020.00338. eCollection 2020. PMID: 32547492

Haffner D, Emma F, et al. [Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia](#). *Nat Rev Nephrol*. 2019 Jul;15(7):435-455.

Briot K, Portale AA, et al. [Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomised phase 3 trial and open-label extension](#). *RMD Open*. 2021 Sep;7(3):e001714. doi: 10.1136/rmdopen-2021-001714. PMID: 34548383

Kayser M, Jain P, et al. *A de novo deleterious PHEX variant with no evidence of X-linked hypophosphatemia*. Abstract 55, 10th International Conference on Children's Bone Health. Dublin, July 2-5, 2002.

Chabchoub G, Uz E, et al. [Analysis of skewed X-chromosome inactivation in females with rheumatoid arthritis and autoimmune thyroid diseases](#). *Arthritis Res Ther*. 2009;11(4):R106. doi: 10.1186/ar2759. Epub 2009 Jul 9. PMID: 19589151

Sarafrazi S, Daugherty SC, et al. [Novel PHEX gene locus-specific database: comprehensive characterization of vast number of variants associated with x-linked hypophosphatemia \(XLH\)](#). *Hum Mutat*. 2022 Feb;43(2):143-157.