

# X-LINKED HYPOPHOSPHATEMIA (XLH)

## DIAGNOSTIC TESTING CONSIDERATIONS



**INCREASED FGF23 ACTIVITY: A LIFETIME OF IMPACT**

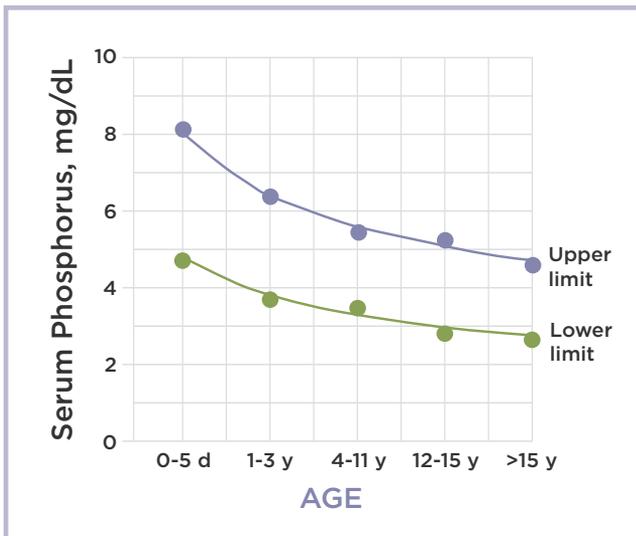
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# XLH IS CHARACTERIZED BY CHRONIC HYPOPHOSPHATEMIA

XLH is a hereditary, progressive, lifelong disorder caused by X-linked dominant variants of the *PHEX* gene that result in increased fibroblast growth factor (FGF23) activity. In children and adults, the hallmarks of XLH are chronic hypophosphatemia (low levels of serum phosphate, 2.5 mg/dL or below) due to this increased FGF23 activity.<sup>1-4</sup>

## NORMAL SERUM PHOSPHORUS LEVELS<sup>2,\*</sup>



Note that normal serum phosphorus levels vary with age and food intake. Therefore, when assessing potential patients, it is important to use age-related reference values and collect *fasting* blood and urine samples.<sup>2,5</sup>

\*Commonly used reference dataset. For other dataset references, see <http://www.xlhnetwork.org/index.php/technical-information/diagnosis-technical-info>

## PRINCIPLES IN DIAGNOSING A HYPOPHOSPHATEMIC DISORDER

- Serum phosphorus levels decline with age. Do not check a child's levels against adult reference ranges<sup>2</sup>
- High urine phosphorus despite low serum phosphorus suggests an FGF23-mediated or intrinsic renal disorder, which can be distinguished by serum 1,25(OH)<sub>2</sub>D levels<sup>6</sup>
- Serum 1,25(OH)<sub>2</sub>D is low or inappropriately normal in XLH, but elevated in non-FGF23-mediated forms of phosphopenic rickets<sup>2,6,7</sup>

1,25(OH)<sub>2</sub>D = 1,25-dihydroxyvitamin D.



## DIAGNOSING XLH

- Diagnosis is typically based on clinical and biochemical findings in combination with family history<sup>2</sup>
- A diagnosis of XLH can be confirmed through genetic testing of the *PHEX* gene and/or additional biochemical testing for elevated levels of circulating FGF23<sup>2,8</sup>



## CHILDREN WITH XLH

- Evaluation of rickets, in combination with a careful assessment of biochemical findings and confirmatory *PHEX* gene and/or circulating FGF23 testing can support an accurate diagnosis<sup>2,6,8</sup>
- In children who present with suspected rickets, differentiate between calcipenic and phosphopenic rickets, and then distinguish the etiology of rickets from other potential disorders to narrow down to XLH (see Differential diagnosis in children presenting with rickets)<sup>6</sup>



## ADULTS WITH XLH

- Adults with XLH most commonly present with pain and stiffness. Radiographic findings of osteomalacia, pseudofractures and fractures, mineralization of tendons or ligaments (such as enthesopathy), or joint space narrowing (evidence of arthritis), as well as family history, should raise suspicion of XLH<sup>1-4</sup>
- Careful assessment of biochemical findings, paired with *PHEX* gene and/or circulating FGF23 testing, can support an accurate diagnosis of XLH<sup>2,8</sup>

## BIOCHEMICAL FINDINGS IN XLH

Biochemical Test	XLH <sup>2,7</sup>
Serum phosphorus	↓
1,25(OH) <sub>2</sub> D	↓ or inappropriately normal
25(OH)D	normal
TmP/GFR	↓
ALP*	↑
Serum calcium	normal
Urinary calcium	normal to ↓
PTH	normal or slightly ↑

\*ALP can be a good marker of skeletal health in children but not necessarily for adults.<sup>2</sup>

### MOST RELEVANT FINDINGS FOR XLH IN CHILDREN<sup>2,6</sup>:

- Low serum phosphorus levels
- Low-to-normal circulating 1,25(OH)<sub>2</sub>D
- Reduced TmP/GFR
- Elevated ALP
- Normal-to-elevated PTH levels

1,25(OH)<sub>2</sub>D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D (calcifediol); ALP = alkaline phosphatase; PTH = parathyroid hormone; TmP/GFR = ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate.



# DIFFERENTIAL DIAGNOSIS IN CHILDREN PRESENTING WITH RICKETS

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**HYPOPHOSPHATASIA** – Rare genetic disorder of alkaline phosphatase activity characterized by bone demineralization.<sup>6</sup> *In contrast to XLH, serum alkaline phosphatase activity is very low.*



**RENAL INSUFFICIENCY** – Bone disease occurs in children with renal insufficiency for many reasons, including reduced formation of 1,25(OH)<sub>2</sub>D, metabolic acidosis, administration of aluminum, and secondary hyperparathyroidism.<sup>6</sup> *Evaluate renal function by measuring serum creatinine.*



**SKELETAL DYSPLASIA** – Skeletal dysplasia (eg, achondroplasia, pseudoachondroplasia, metaphyseal chondrodysplasia) can also cause bilateral, symmetric bowed legs similar to those of rickets. However, *serum inorganic phosphorus and PTH concentrations usually are normal in children with skeletal dysplasia.*<sup>6</sup>



**LIVER DISEASE** – Elevation of serum alkaline phosphatase activity can be caused by liver disease. Confirmation can be done by *measuring liver enzymes (serum ALT, AST, and GGT).*<sup>6</sup>



**TRANSIENT HYPERPHOSPHATASEMIA** – *Elevation of serum alkaline phosphatase but normal liver enzymes and no radiographic evidence of rickets may be indicative of transient hyperphosphatasemia of infancy and early childhood. This usually benign condition may arise after a minor infectious illness.*<sup>6</sup>



**PRIMARY HYPOPARATHYROIDISM** – *Causes marked hypocalcemia, but is usually not associated with rickets. Suggests that low serum phosphorus and/or PTH itself may play roles in mediating the growth plate lesion.*<sup>6</sup>



**BLOUNT DISEASE** – A pathologic varus deformity of the knee resulting from disruption of normal cartilage growth at the medial aspect of the proximal tibial physis. *It can be distinguished from rickets by distinct radiographic findings and normal serum biochemistry values.*<sup>6</sup>

# IN PATIENTS WITH XLH, CHRONIC HYPOPHOSPHATEMIA DUE TO INCREASED FGF23 ACTIVITY RESULTS IN POOR SKELETAL, MUSCULAR, AND DENTAL HEALTH, AS WELL AS IMPAIRED PHYSICAL FUNCTION.<sup>1,2</sup>

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## WHEN DIAGNOSING XLH, REMEMBER:

- Assess clinical findings
- Evaluate age-specific biochemical findings
- Consider family history
- Differentiate rickets in children
- Consider confirming a diagnosis through genetic testing for *PHEX* gene variants

**REFERENCES:** 1. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;26(7):1381-1388. 2. Ruppe MD. X-linked hypophosphatemia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. 3. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol.* 2019;15(7):435-455. doi:10.1038/s41581-019-0152-5. 4. Imel EA, Econs MJ. Approach to the hypophosphatemic patient. *J Clin Endocrinol Metab.* 2012;97(3):696-706. 5. Bansal VK. Serum inorganic phosphate. In: Walker HK, Hall WD, Hurst JW, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations.* 3rd ed. Boston: Butterworths; 1990. 6. Carpenter T. Overview of rickets in children. In: Post TW, ed. *UpToDate.* Waltham, MA: UpToDate; 2018. <https://www.uptodate.com/contents/overview-of-rickets-in-children>. Accessed March 11, 2019. 7. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol.* 2013;28(4):595-603. 8. Jonsson KB, Zahradnik R, Larsson T, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med.* 2003;348(17):1656-1663.