X-LINKED HYPOPHOSPHATEMIA (XLH)

DIAGNOSTIC TESTING CONSIDERATIONS

INCREASED FGF23 ACTIVITY: A LIFETIME OF IMPACT

TODDLER • ADOLESCENT • YOUNG ADULT • MATURE ADULT
XLH IS CHARACTERIZED BY CHRONIC HYPOPHOSPHATEMIA

XLH is a hereditary, progressive, and lifelong disorder caused by X-linked dominant variants of the \textit{PHEX} gene that result in increased fibroblast growth factor 23 (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.\textsuperscript{1, 4}

DIAGNOSING XLH

- Diagnosis is typically based on clinical and biochemical findings in combination with family history\textsuperscript{2}
- A diagnosis of XLH can be confirmed through genetic testing of the \textit{PHEX} gene and/or additional biochemical testing for elevated levels of circulating FGF23\textsuperscript{2, 5}

BIOCHEMICAL FINDINGS IN XLH

<table>
<thead>
<tr>
<th>Biochemical Test</th>
<th>XLH\textsuperscript{2, 6}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphorus</td>
<td>↓</td>
</tr>
<tr>
<td>1,25(OH)\textsubscript{2}D</td>
<td>↓ or inappropriately normal</td>
</tr>
<tr>
<td>25(OH)\textsubscript{2}D</td>
<td>normal</td>
</tr>
<tr>
<td>TmP/GFR</td>
<td>↓</td>
</tr>
<tr>
<td>ALP*</td>
<td>↑</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>normal</td>
</tr>
<tr>
<td>Urinary calcium</td>
<td>normal to ↓</td>
</tr>
<tr>
<td>PTH</td>
<td>normal or slightly ↑</td>
</tr>
</tbody>
</table>

Individual biochemical findings can add value to understanding the clinical picture over time but should not be relied upon as a solitary indicator or global markers, especially in the short term, and should be used in the context of serum phosphorus and along with other clinical parameters for prognosis.\textsuperscript{1}

PRINCIPLES IN DIAGNOSING A HYPOPHOSPHATEMIC DISORDER

- Serum phosphorus levels decline with age. Do not check a child’s levels against adult reference ranges\textsuperscript{3}
- High urine phosphorus despite low serum phosphorus suggests an FGF23-mediated or intrinsic renal disorder, which can be distinguished by serum 1,25(OH)\textsubscript{2}D levels\textsuperscript{7}
- Serum 1,25(OH)\textsubscript{2}D is low or inappropriately normal in XLH, but elevated in non-FGF23-mediated forms of phosphopenic rickets\textsuperscript{2, 4, 7}

NORMAL SERUM PHOSPHORUS LEVELS\textsuperscript{2, 8}

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 d</td>
<td>0.5 mg/dL</td>
<td>1.5 mg/dL</td>
</tr>
<tr>
<td>6-11 y</td>
<td>4.0 mg/dL</td>
<td>6.0 mg/dL</td>
</tr>
<tr>
<td>&gt;12 y</td>
<td>5.0 mg/dL</td>
<td>7.0 mg/dL</td>
</tr>
</tbody>
</table>

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.\textsuperscript{2, 8}

NORMAL SERUM ALKALINE PHOSPHATASE LEVELS\textsuperscript{9}

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 d</td>
<td>10 U/L</td>
<td>20 U/L</td>
</tr>
<tr>
<td>1-7 d</td>
<td>100 U/L</td>
<td>200 U/L</td>
</tr>
<tr>
<td>8-16 y</td>
<td>200 U/L</td>
<td>400 U/L</td>
</tr>
<tr>
<td>&gt;17 y</td>
<td>200 U/L</td>
<td>400 U/L</td>
</tr>
</tbody>
</table>

\*ALP can be a good marker of skeletal health in children but not necessarily for adults.\textsuperscript{2}
†Commonly used reference dataset. For other dataset references, see http://www.xlhnetwork.org/index.php/technical-information/diagnosis-technical-info.
1,25(OH)\textsubscript{2}D = 1,25-dihydroxy vitamin D; 25(OH)\textsubscript{2}D = 25-hydroxy vitamin D (calcifediol); ALP = alkaline phosphatase; PHEX = phosphate-regulating endopeptidase homolog, X-linked; PTH = parathyroid hormone; TmP/GFR = ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate.
DIFFERENTIAL DIAGNOSIS IN CHILDREN PRESENTING WITH RICKETS

- 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.2,5,7
- 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.7

**HYPOPHOSPHATASIA** – Rare genetic disorder of alkaline phosphatase activity characterized by bone demineralization.7 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)2D, metabolic acidosis, administration of aluminum, and secondary hyperparathyroidism.7 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.7

**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).7

**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.7

**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.7

**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.7

1,25(OH)2D = 1,25-dihydroxy vitamin D; ALP = alkaline phosphatase; FGF23 = fibroblast growth factor 23; Ca = calcium; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PHEX = phosphate-regulating endopeptidase homolog, X-linked; PTH = parathyroid hormone; GGT = gamma-glutamyl transpeptidase.
DIFFERENTIAL DIAGNOSIS IN ADULTS PRESENTING WITH RHEUMATIC/ORTHOPEDIC SYMPTOMS

- Adults with XLH most commonly present with pain and stiffness. Radiographic findings of osteomalacia, pseudo fractures 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.4
- Careful assessment of biochemical findings, paired with PHEX gene and/or circulating FGF23 testing, can support an accurate diagnosis of XLH.1-4

OSTEOPOROSIS/OSTEOPENIA – Increased bone resorption and/or decreased bone formation leads to porous, brittle bones that are at higher risk for fractures. Fractures in XLH, in contrast, are caused by osteomalacia, a softening of the bones due to mineral loss. Patients with osteoporosis present with normal serum phosphorus and ALP compared to patients with XLH.10,11

ANKYLOSING SPONDYLITIS – Chronic inflammatory arthritis of the axial skeleton that causes joint pain and stiffness in the back and sacroiliac joint. Both ankylosing spondylitis and XLH are associated with increased serum ALP. Hypophosphatemia is key to the diagnosis of XLH while radiographic imaging and the presence of HLA-B27 are used to diagnose ankylosing spondylitis.12,13

RHEUMATOID ARTHRITIS – Characterized by symmetric, inflammatory disease with multiple joint involvement, positive rheumatoid factor (RF), and elevated C-reactive protein (CRP). Patients with XLH will not have positive RF or elevated CRP.14

OSTEOARTHRITIS (OA) – Typically presents over time in middle-aged and older patients. OA can be diagnosed through clinical presentation and synovial fluid analysis. Serum phosphate levels are not affected by OA.15

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) – Can affect multiple organ systems. SLE manifests as chronic inflammation due to the production of antibodies to nuclear and cytoplasmic antigens. Joint pain is common in both XLH and SLE. Diagnosis of SLE is based on the presence of a wide range of clinical presentations combined with immunologic testing.16-18

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH) – A common disease characterized by calcification and ossification. DISH typically causes pain and stiffness in the thoracic and cervical spine, but it can also affect joints throughout the body. DISH can be diagnosed based on a patient's medical history and confirmed with X-rays.19,20

FIBROUS DYSPLASIA OF BONES – A noninherited bone disorder caused by a genetic variation in GNAS1 that arises during fetal development. The resulting replacement of normal bone with abnormal fibrous tissue can cause pain, fractures, and other skeletal abnormalities based on which bones are affected. About 20% to 30% of XLH cases are spontaneous, while fibrous dysplasia is always a spontaneous genetic mutation.21-23

TUMOR-INDUCED OSTEOMALACIA (TIO) – An acquired form of hypophosphatemia caused by the secretion of FGF23 by slow-growing mesenchymal tumors. Like XLH, adult patients with TIO present with phosphate wasting without hypercalciuria and progressive muscle and bone pain. Onset can occur at any age but the majority of patients with TIO are adults.2

HYPOPHOSPHATASIA (HPP) – Rare genetic disorder of alkaline phosphatase activity characterized by bone demineralization.24 In contrast to XLH, serum alkaline phosphatase activity is very low.

RENAL INSUFFICIENCY – Bone disease occurs with renal insufficiency for many reasons, including reduced formation of 1,25(OH)2D, metabolic acidosis, administration of aluminum, and secondary hyperparathyroidism.24 Evaluate serum creatinine for underlying renal dysfunction.

LIVER DISEASE – Elevation of serum alkaline phosphatase activity can be caused by liver disease. Assess liver panel (serum ALT, AST, and GGT) for underlying liver disease.24

RENAL FANCONI SYNDROME – A rare disorder in which a defect in renal proximal tubule transport leads to malabsorption of multiple substances. Phosphate wasting can be noted in both Fanconi Syndrome and XLH. Fanconi Syndrome is determined by glycosuria, bicarbonaturia, and/or amino aciduria.2

VITAMIN D DEFICIENCY – Deficiency in vitamin D causes hypocalcemia and hypophosphatemia in patients, which leads to rickets and osteomalacia. Decreased renal function can also be a cause of vitamin D deficiency and should be evaluated in patients. XLSH should be evaluated in patients with vitamin D deficiency that present with low serum phosphate and normal or mildly elevated PTH.25,26

1,25(OH)2D = 1,25-dihydroxy vitamin D; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FGF23 = fibroblast growth factor 23; GGT = gamma-glutamyl transpeptidase; PHEX = phosphate-regulating endopeptidase homolog, X-linked; GNAS1 = guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1; HLA-B27 = human leukocyte antigen B27; PTH = parathyroid hormone.
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.¹,²

WHEN DIAGNOSING XLH, REMEMBER:

- Assess clinical findings
- Evaluate age-specific biochemical findings
- Consider family history
- Differentiate rickets in children and rheumatic/orthopedic symptoms in adults
- Consider confirming a diagnosis through genetic testing for PHEX gene variants


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