HEREDITARY, PROGRESSIVE, AND LIFELONG
X-LINKED HYPOPHOSPHATEMIA (XLH)

INCREASED FGF23 ACTIVITY: A LIFETIME OF IMPACT

TODDLER • ADOLESCENT • YOUNG ADULT • MATURE ADULT
DISEASE OVERVIEW

X-LINKED HYPOPHOSPHATEMIA (XLH) IS A HEREDITARY, PROGRESSIVE, AND LIFELONG DISEASE

XLH is a chronic disease that impacts children and adults throughout their lives.

Rickets and osteomalacia due to chronic hypophosphatemia result in poor skeletal, muscular, and dental health.

XLH is inherited within families, but about 20% to 30% of cases may arise spontaneously.

Prevalence: 1 in 20,000 to 1 in 25,000 live births.

XLH is characterized by chronic hypophosphatemia due to increased fibroblast growth factor (FGF23) activity that impacts patients in many ways, resulting in:

- Rickets and osteomalacia, the sources of compounding symptoms in XLH
- Pain and progressive skeletal defects, muscular dysfunction, and dental abnormalities
- Limitations in physical function and mobility

XLH has also been known by patients and health care providers as:

- X-linked hypophosphatemic rickets
- Hereditary hypophosphatemic rickets
- Familial hypophosphatemic rickets
- Vitamin D-resistant rickets (VDRR)
- Vitamin D-resistant osteomalacia
- X-linked vitamin D-resistant rickets
- Hypophosphatemic rickets
- Hypophosphatemic vitamin D-resistant rickets (HPDR)
- X-linked rickets (XLR)
- Genetic rickets
- Familial hypophosphatemia
1 INCREASED CIRCULATING FGF23

In XLH, an X-linked dominant genetic variant of the PHEX gene causes increased FGF23 activity, which leads to chronic hypophosphatemia.\(^{1,2,10}\)

2 DECREASED RENAL PHOSPHATE REABSORPTION AND CALCITRIOL PRODUCTION

Increased FGF23 decreases renal phosphate reabsorption, which increases urinary phosphate excretion and decreases calcitriol production.\(^{1,10}\)

3 DECREASED INTESTINAL PHOSPHATE ABSORPTION

Decreased calcitriol reduces intestinal phosphate absorption.\(^{1,10}\)

In normal homeostasis, FGF23 is a protein hormone mainly produced by osteocytes in the bones to regulate serum phosphate levels.\(^{10}\)

Increased FGF23 activity leads to chronic hypophosphatemia, which manifests as rickets and osteomalacia in children and as osteomalacia in adults.

In XLH, increased FGF23 activity is caused by a genetic variation, resulting in lifelong and progressive symptoms from childhood to adulthood.
**CLINICAL PRESENTATION AND DISEASE PROGRESSION — CHILDREN**

XLH IMPAIRS PHYSICAL FUNCTION AND HAS A LONG-TERM NEGATIVE IMPACT ON CHILDREN THAT CAN CONTINUE INTO ADULTHOOD

Rickets and osteomalacia are the underlying sources of symptoms that will progress throughout adulthood and can limit growth and physical function in children with XLH.\(^1,2,11\)

**SIGNS AND SYMPTOMS OF XLH IN CHILDREN\(^1,2,6-8,11,12\)**

- **CRANIOSYNOSTOSIS AND CHIARI MALFORMATIONS**
- **SKELETAL PAIN AND MUSCLE STIFFNESS**
- **DENTAL ABScessoES**
- **KNOCK-KNEES**
- **WINDSWEPT DEFORMITIES**
- **SHORT STATURE**
- **RICKETS AND OSTEOMALACIA**
- **BOWED LEGS**

An early and accurate diagnosis of XLH is essential to appropriate disease management

Children can present with symptoms that vary in severity, which may include\(^1\):

**SKELETAL DEFECTS**
- Rickets and osteomalacia can lead to lower extremity deformities\(^2,11\)
- Bone and joint pain may accompany rickets and osteomalacia\(^2,4\)
- Cranial defects such as Chiari malformations and craniosynostosis may also manifest\(^2,11\)

**MUSCULAR DYSFUNCTION**
- Muscular dysfunction such as muscle pain, stiffness, and weakness\(^4,11\)
- Muscle weakness can result in gait disturbances\(^7,11\)

**DENTAL ABNORMALITIES**
- Dental abscesses\(^1,11\)
- Tooth loss\(^11\)
Adults with XLH may not associate their pain with their previous diagnosis and may present with:

**SKELETAL DEFECTS**
- Bone and joint pain, as well as fatigue, can manifest because of osteomalacia\(^2,5,11\)
- Pseudofractures and fractures\(^1,2,11\)
- Short stature and lower extremity deformities\(^2,11\)
- Enthesopathy or calcification of the tendons\(^1,2,11\)
- Osteoarthritis\(^7,11\)

**MUSCULAR DYSFUNCTION**
- Compounding muscular dysfunction, such as muscle pain, stiffness, weakness, and gait disturbances\(^7,11\)

**DENTAL ABNORMALITIES**
- Dental abscesses continue to manifest in adults and may subsequently develop into periodontitis or result in tooth loss\(^11\)
Rickets, osteomalacia, and lower extremity deformities that result from chronic hypophosphatemia create a significant burden for children, affecting their daily lives.\(^4\,11\)

The ongoing osteomalacia can result in pain, limitations in range of motion, and even disability.\(^5\,11\)

**BURDEN OF DISEASE — CHILDREN**

**XLH LIMITS GROWTH AND PHYSICAL FUNCTION IN CHILDREN**

Data taken from a burden-of-disease study conducted in 71 pediatric patients with XLH.

**DELAYED GROWTH RESULTING IN SHORT STATURE**\(^11,13\)

**PAIN AND LIMITED PHYSICAL FUNCTION**\(^4\)

**LIMITED RANGE OF MOTION AND PAIN**\(^1\)

Data is taken from a burden-of-disease study conducted in 71 pediatric patients with XLH.

**BURDEN OF DISEASE — ADULTS**

**XLH LIMITS PHYSICAL MOBILITY OF ADULTS**

In adults with XLH, on average approximately 50% have their first low-trauma fracture at 26.5 years of age, and they have an average of 3.7 low-trauma fractures at time of survey.\(^1\)

**INCREASED RISK OF FRACTURES AND PSEUDOFRACTURES**\(^2,5,6\)

**LIMITED RANGE OF MOTION AND PAIN**\(^1\)

Data is taken from an international burden-of-disease study conducted in 165 adult patients with XLH.
DIAGNOSIS AND ASSESSMENT

A DIAGNOSIS OF XLH IS TYPICALLY BASED ON CLINICAL AND BIOCHEMICAL FINDINGS IN COMBINATION WITH FAMILY HISTORY

WITH KNOWN FAMILY HISTORY OF XLH

XLH is inherited in an X-linked dominant pattern. In a family with a history of XLH, screen for other family members. This can help you identify previously undisagnosed individuals.

WITHOUT A KNOWN FAMILY HISTORY

About 20% to 30% of XLH cases are spontaneous. Ask about his/her medical history of short stature, rickets, osteomalacia, osteoarthritis, and dental abscesses, which may indicate XLH.

A DIAGNOSIS OF XLH CAN BE CONFIRMED THROUGH GENETIC TESTING FOR VARIANTS OF THE PHEX GENE

FAMILY HISTORY

AFFECTED FATHER

All daughters affected, no sons affected

AFFECTED MOTHER

Each child has a 50% chance of inheriting XLH, regardless of sex

CLINICAL FINDINGS

PREDOMINANT FINDINGS IN CHILDREN

Rickets, lower extremity bowing, leg deformities, pain, short stature, and gait disturbances. Confirm skeletal findings through radiography. Other signs and symptoms may also include dental abscesses, craniosynostosis, and Chiari malformations.

PREDOMINANT FINDINGS IN ADULTS

Adults with XLH may present with osteomalacia manifesting as bone and muscle pain, enthesopathy, fractures, and pseudofractures. Other signs and symptoms may also include waddling gait, dental abscesses, and hearing loss.

BIOCHEMICAL FINDINGS

Include age- and gender-normalized levels of serum phosphorus in metabolic panels for an accurate diagnosis. Low phosphate levels and low TmP/GFR ratio are the most relevant biochemical findings for XLH.

Biochemical Test | XLH
---|---
Serum phosphorus | ↓ or inappropriately normal
25(OH)D | normal
TmP/GFR | ↓
ACP | ↑
Serum calcium | normal
Urinary calcium | normal or slightly ↑
PTH | normal or slightly ↑

Other biochemical tests that may be useful for establishing the diagnosis of XLH include serum alkaline phosphatase (ALP) levels and FGFR3 levels. Alkaline phosphatase can be a good marker of skeletal health in children but not necessarily for adults.

1,25(OH)2D = 1,25-dihydroxyvitamin D3 (calcitriol); 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; XLH = X-linked hypophosphatemia.
XLH RESOURCES FOR YOU AND YOUR PATIENTS

XLHLink - information, tools, and resources designed for people with XLH, their caregivers, and their health care team
XLHLink.com

The XLH Network - A worldwide community of XLH patients, parents, caregivers, and medical professionals
XLHNetwork.org

Biomedema - An online disease-monitoring program for patients with X-linked hypophosphatemia (XLH) and other chronic hypophosphatemic disorders
BeyondXLH.com

GARD Genetic and Rare Diseases Information Center (GARD) - A list of rare diseases and related terms to help people find reliable information
RareDiseases.info.nih.gov

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XLHLink - information, tools, and resources designed for people with XLH, their caregivers, and their health care team
XLHLink.com

National Organization for Rare Disorders (NORD) - A patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them
RareDiseases.org

The XLH Network - A worldwide community of XLH patients, parents, caregivers, and medical professionals
XLHNetwork.org

Beyond XLH - An online disease-monitoring program for patients with X-linked hypophosphatemia (XLH) and other chronic hypophosphatemic disorders
BeyondXLH.com

Global Genes - A rare disease patient advocacy organization that works to build awareness, educate the global community, and provide connection and resources
GlobalGenes.org

REFERENCES

5. Skrinar A, Marshall A, San Martinez J, Drozak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: ENDO 2015; March 5-8, 2015; San Diego, CA.
XLH is a hereditary, progressive, and lifelong disease.

FGF23 is the root cause of XLH.

Rickets and osteomalacia are the underlying sources of compounding and progressive symptoms of XLH.

XLH poses a significant burden on the daily lives of children and adults due to impaired physical function.

Family history, clinical findings, and biochemical tests can be used to establish a diagnosis of XLH.

Learn more at XLHLink.com