XLH
(X-LINKED HYPOPHOSPHATEMIA)

XLH is an X-linked dominant disorder due to a pathogenic variant in the *PHEX* gene. XLH is characterized by renal phosphate wasting and impaired vitamin D metabolism. XLH can present in childhood with lower limb bowing and short stature. XLH is sometimes first identified in adulthood due to short stature, bone pain and fractures.

XLH TREATMENT OPTIONS

XLH is managed in childhood with phosphate and active vitamin D replacement or anti-FGF23 therapy (burosumab). Some patients will consider stopping treatment in adulthood, typically because of side effects of treatment (with phosphate and active vitamin D) or lack of access to the newer medication, burosumab. If treatment is discontinued and the adult with XLH develops worsening bone pain, functional limitations or osteomalacic fractures, re-initiation of treatment should be considered. Generally speaking, XLH is a lifelong condition with potential for cumulative, multi-system co-morbidities; therefore, treatment is typically considered life-long as well.

The goals of treatment include improving bone pain and physical function, normalizing serum alkaline phosphatase concentrations, and improving serum phosphate levels. While normalization of serum phosphate levels is achievable in many individuals on burosumab, this is not a goal of conventional therapy due to the unfavorable effects of phosphate normalization on the kidneys and parathyroid glands.

XLH MONITORING

Individuals should be monitored clinically every 6-12 months (the exception to this is very young children, where follow-up is recommended more frequently). A careful history and physical exam should check for the following:

- Bone pain and/or history of fracture(s)
- Muscle weakness
- Osteoarthritis, gait problems or limitations to joint range of motion
- High blood pressure
- Dental abscesses, caries, periodontitis
- Neurological symptoms, including those linked to the Chiari 1 malformation, craniosynostosis and/or syringomyelia (e.g. headaches worse with valsalva maneuvers, radiating neck pain, arm weakness or numbness, gait or visual disturbances)
- Sensorineural hearing loss, tinnitus and vertigo

Individuals with XLH on treatment (conventional or burosumab) should undergo regular bloodwork every 4-6 months and annual or biennial imaging. This includes:

Biochemical Monitoring:

- Serum phosphate, calcium, albumin, alkaline phosphatase, parathyroid hormone, creatinine
- Serum 25-hydroxyvitamin D (aim for a 25-hydroxyvitamin D level ≥ 50 nmol/L)

Imaging monitoring:

- Children: wrists and knee x-rays for rickets severity score
- Both children and adults: x-rays for lower limb malalignment, renal ultrasound for nephrocalcinosis on treatment
- Brain MRI or Computed Tomography (CT) scanning if concerning neurologic symptoms

CARDS
Canadian Alliance for Rare Disorders of the Skeleton

CANADIAN XLH NETWORK

CCCBH
Canadian Consortium for Children's Bone Health

XLH-RELATED HEALTH ISSUES

XLH is a multi-systemic disorder and should be managed by a multidisciplinary team. Team members to consider include:

- Endocrinologist
- Nephrologist
- Nurse
- Dentist
- Mental health expert
- Audiologist
- Physiotherapist
- Occupational Therapist
- Neurosurgeon
- Orthopedic surgeon

Musculoskeletal

XLH can have long term complications including enthesopathies (stiffening of tendons and ligaments), osteophytes (bone spurs), spinal stenosis, early osteoarthritis, and pseudofractures/osteomalacic fractures. If adults with XLH develop worsening or focal limb pain, consider an X-ray for pseudofracture/osteomalacic fracture. If this type of fracture is present, it is an indication to resume therapy, or to switch from conventional therapy to burosumab.

Cranial/Neurologic

Chiari 1 malformations, craniosynostosis, and syringomyelia are seen more frequently in XLH than the general population. Headaches worsening with valsalva maneuvers, radiculopathy including radiating neck pain, upper arm numbness or weakness, signs of cranial nerve impingement, and gait or visual disturbances may be signs of a cranial/neurologic abnormality. Consider brain MRI, skull CT and/or spine MRI if symptoms are present, with neurosurgery referral as appropriate.

Renal

Individuals with XLH have higher rates of hypertension than the average population and hypertension should be treated as per age-appropriate guidelines. Nephrocalcinosis is a common complication in XLH, particularly with phosphate and active vitamin D supplementation. Patients receiving medical therapy for XLH should have periodic monitoring for nephrocalcinosis.

Dental

XLH can affect the teeth, causing undermineralization of the tooth's dentin and a predisposition to bacterial invasion. There is a high frequency of dental abscess, caries, periodontitis, and early loss of teeth.
Dentists should monitor for enlarged pulp chambers, dental abscesses, and periodontal disease.

Hearing

Individuals with XLH have an increased risk of hearing problems. Individuals with XLH should be referred to audiology and/or Ear Nose and Throat doctors when tinnitus, vertigo, and/or hearing loss are reported.

Mental health

Chronic pain is a frequent complication of XLH, particularly in adults. It is important to recognize the impact of chronic pain including ongoing assessment of functional impairments. We caution against routine use of opioids for pain in XLH as this does not address the underlying osteomalacia of XLH and increases the risk of opioid dependency.

FAMILY PLANNING

XLH is an X-linked dominant condition; all of the daughters and none of the sons of an affected father will inherit the condition. Females with XLH will have a 50% chance of passing along the condition to both their daughters and sons. Adults with XLH considering family planning may benefit from seeing a genetic counselor. It is unclear what the impacts of treatment are in pregnancy and treatment should involve an informed discussion between pregnant women with XLH and knowledgeable XLH care providers. Women with XLH who are pregnant should have their biochemistry (see XLH monitoring section) and bone pain monitored closely. Genetic testing should be offered as soon as possible for newborns of parents with XLH along with referrals to pediatric XLH providers, typically endocrinology or nephrology.

Informative Brochure for
HEALTHCARE PROVIDERS

XLH
(X-LINKED HYPOPHOSPHATEMIA)

XLH is an X-linked dominant disorder due to a PHEX variant. XLH is characterized by renal phosphate wasting and impaired vitamin D metabolism. XLH can present in childhood with lower limb bowing and short stature. XLH is sometimes identified in adulthood due to shorter stature, bone pain and fractures. XLH is managed in childhood with phosphate and active vitamin D replacement or anti-FGF23 therapy (burosumab). Treatment in childhood improves rickets healing, lower limb deformity, and growth. Treatment in adulthood improves bone pain and promotes healing of fractures arising from poor bone mineralization (osteomalacia).

Multi-Disciplinary Team

XLH is a multi-systemic disorder and should be managed with a multidisciplinary team including a physician familiar with the condition.

Team members to consider include:

- Endocrinologist
- Nephrologist
- Nurse
- Dentist
- Audiologist
- Physiotherapist
- Occupational therapist
- Orthopedic surgeon
- Neurosurgeon
- Mental health expert

XLH Monitoring

Individuals with XLH should have ongoing monitoring. This includes:

Biochemical monitoring:

- Serum phosphate, calcium, albumin, alkaline phosphatase, parathyroid hormone, creatinine
- Serum 25-hydroxyvitamin D (aim for level of 50 nmol/L or above)

Imaging monitoring:

- ***Children:*** wrists and knee x-rays for rickets severity score
- ***Both children and adults:*** x-rays for lower limb malalignment, renal ultrasound for nephrocalcinosis on treatment
- Brain MRI or Computed Tomography (CT) scanning if concerning neurologic symptoms such as headaches, neck pain, gait or visual disturbances

Family Planning

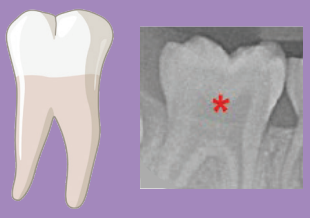
XLH is an X-linked dominant condition. All of the daughters and none of the sons of an affected father will inherit the condition. Females with XLH will have a 50% chance of passing along the condition to both their daughters and sons. Adults with XLH considering family planning may benefit from seeing a genetic counselor.

Women with XLH who are pregnant should be monitored closely for phosphate abnormalities and bone pain. Genetic testing should be offered as soon as possible for newborns of parents with XLH along with referrals to pediatric XLH providers, typically endocrinology or nephrology

COMPLICATIONS THAT CAN OCCUR IN XLH

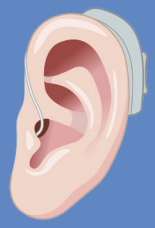
Dental

XLH affects the teeth as well as the bones, resulting in dental abscesses, caries, periodontitis, and early tooth loss. Dentists should monitor for enlarged pulp chambers, dental abscesses and periodontal disease.



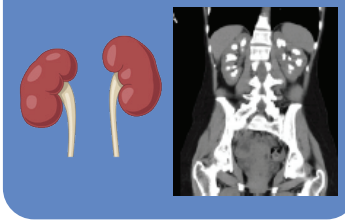
Hearing

Individuals with XLH have an increased risk of hearing problems. This can present as tinnitus, vertigo, and/or hearing loss. Individuals should be referred to audiology if these symptoms develop.



Renal

Individuals with XLH have higher rates of hypertension than the average population. Blood pressure should be monitored closely and treated appropriately. Patients receiving medical therapy for XLH should have periodic monitoring for nephrocalcinosis.



Mental Health & Chronic Pain

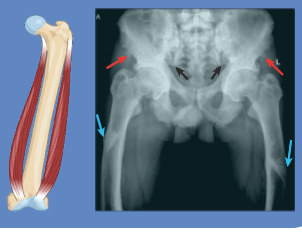
Chronic pain is common in XLH. It is important to recognize the impact of chronic pain with ongoing assessment of pain and functional impairment. Options to treat pain in XLH are available.

Cranial/ Neurological

Chiari 1 malformations, craniosynostosis and syringomyelia are seen more frequently in XLH than the general population. These are potentially serious complications of XLH that can occur in children and adults. Headaches worse with valsalva maneuvers, radiating neck pain, arm numbness or weakness, or gait or visual disturbances may be signs of neurocranial abnormalities and imaging for these complications may be considered.

Musculoskeletal

Musculoskeletal complications include enthesopathies, osteophytes, spinal stenosis, early osteoarthritis, and pseudofractures/osteomalacic fractures. If adults with XLH develop worsening or focal bone pain, consider an X-ray for pseudofracture/osteomalacic fracture.



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