XLH is a rare, hereditary, progressive and lifelong phosphate wasting disorder that leads to renal phosphate wasting and chronic hypophosphataemia.\(^1,2\)

XLH is caused by mutations in the \textit{PHEX} gene that leads to excess FGF23 activity.\(^2\)

The diagnosis of XLH is frequently delayed, which has a detrimental effect on patient outcomes.\(^1\)

If you see a newborn or infant with a family history of rickets or a phosphate wasting disorder, consider referral. Other red flags for XLH include:

1. **BOWING IN LOWER LIMBS**
   XLH can impair healthy bone mineralisation, leading to rickets and progressive lower limb deformities in children.\(^1-3\) Bowing deformities of the leg typically present during the second year of life, \(^1-3\) however, appropriate treatment can improve mobility and growth outcomes.\(^4\)

2. **DELAYED WALKING WITH A WADDLING GAIT**
   XLH can impact motor development and mobility.\(^1,5\) During the second year of life, children with XLH typically present with delayed walking and an abnormal, or ‘waddling’ gait.\(^1,5\)

3. **PAIN IN LEGS**
   Bone, joint and muscle pain are highly prevalent in children with XLH and frequently affect the lower limbs.\(^5\)

4. **SHORT STATURE**
   In XLH, impaired limb growth with relatively preserved trunk growth results in disproportionate short stature. Decreased growth velocity is one of the main clinical symptoms of XLH.\(^1\)

5. **ABNORMAL HEAD SHAPE**
   Craniosynostosis is a condition associated with XLH in which one or more of the fibrous sutures in a very young skull prematurely fuses by turning into bone.\(^1\) This may lead to an abnormal head shape in children.

The above signs and symptoms may be caused by XLH.
Consider referral to a paediatrician.
In the presence of red flag signs or symptoms, the following investigations and assessments can help confirm a diagnosis of XLH

**FAMILY HISTORY**
- A positive family history can help confirm a diagnosis of XLH
- Any first-generation family member of a patient with XLH should be investigated for XLH; sons of males are not affected
- Mutational analysis of the \textit{PHEX} gene can help in cases with a negative family history (approx. one-third of patients)

**PHYSICAL EXAMINATION**
- A detailed clinical evaluation should include evidence of:\textbullet Rickets
\textbullet Growth failure
\textbullet Dental abnormalities
\textbullet Craniosynostosis

**RADIOLOGICAL EXAMINATION**
- Consider performing radiography of the knees and/or wrists and/or ankles to confirm a diagnosis of rickets\textsuperscript{1}

**RED FLAG FINDINGS**
- Rickets characterised by cupped and flared metaphyses and widened and irregular physes (growth plates) of the long bones\textsuperscript{1,3}

**BIOCHEMICAL MEASURES**

\begin{tabular}{|l|c|c|}
\hline
Measure & Nutritional rickets & XLH \\
\hline
Calcium & N, ↓ & N \\
Serum phosphate & N, ↓ & ↓ \\
Urinary phosphate & \textit{Varies} & ↑ \\
ALP & ↑↑↑, ↑↑ & ↑, ↑↑ \\
25(OH)D & ↓↓, N & N \\
\hline
\end{tabular}

N, normal; ↑, elevated; ↑↑ or ↑↑↑, very elevated.

IF XLH IS SUSPECTED, REFER TO THE APPROPRIATE PAEDIATRIC CENTRE (endocrinology, paediatric nephrology or paediatric bone disease according to your local guidelines)

References

This leaflet has been developed in collaboration with experts from the XLH Link Working Group. October 2019. KKI/INT/CYS/0003.