RED FLAG SIGNS AND SYMPTOMS OF X-LINKED HYPOPHOSPHATAEMIA (XLH) IN PAEDIATRIC PATIENTS

This leaflet has been developed in collaboration with experts from the XLH Link Working Group.

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 *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:

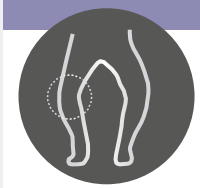
1. BOWING IN LOWER LIMBS

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.

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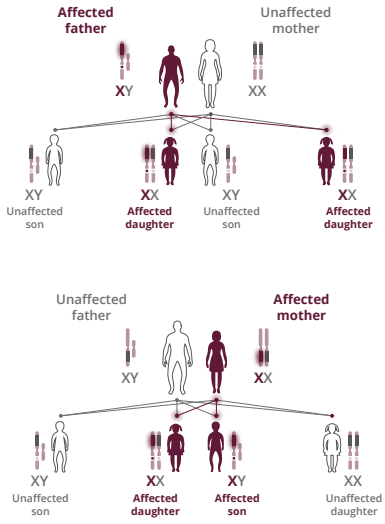
In the presence of red flag signs or symptoms, the following investigations and assessments can help confirm a diagnosis of XLH

Inheritance pattern



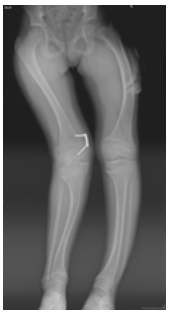
FAMILY HISTORY

- 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 *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:[1]
  - Rickets
  - Growth failure
  - Dental abnormalities
  - Craniosynostosis

RADIOLOGICAL EXAMINATION



Legs of a paediatric patient with XLH

- Consider performing radiography of the knees and/or wrists and/or ankles to confirm a diagnosis of rickets[1]

RED FLAG FINDINGS

- Rickets characterised by cupped and flared metaphyses and widened and irregular physes (growth plates) of the long bones[1,3]

BIOCHEMICAL MEASURES

Selected biochemical characteristics of nutritional rickets and XLH – *see publication for full table*[1]

Measure	Nutritional rickets	XLH
Calcium	N, ↓	N
Serum phosphate	N, ↓	↓
Urinary phosphate	*Varies*	↑
ALP	↑↑↑	↑,↑↑
25(OH)D	↓↓, N	N

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

1. Haffner D, et al. *Nat Rev Nephrol*. 2019 Jul;15(7):435-455; **2.** Beck-Nielsen SS, et al. *Orphanet J Rare Dis*. 2019;14(1):58; **3.** Carpenter TO, et al. *J Bone Miner Res*. 2011;26:1381–8; **4.** Imel EA, et al. *Lancet*. 2019;393:2416–27. **5.** Skrinar A, et al. *J Endocr Soc*. 2019 [Acccepted manuscript].

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