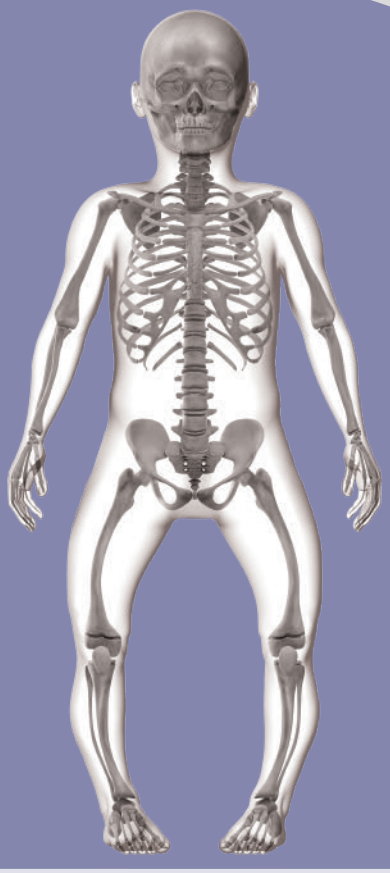
FOR PHYSICIANS

WHAT IS XLH?

PAEDIATRIC features[1]

- Delayed and disproportionate growth
- Craniosynostosis
- Rickets
- Delayed motor development and gait abnormalities
- Short stature
- Deformity of weight-bearing limbs
- Tooth abscesses
- Osteomalacia
- Bone and joint pain
- Muscle pain and weakness
- Chiari malformation
- Diminished quality of life including psychosocial impact



As a primary care physician, what should you know about X-linked hypophosphataemia (XLH)?

- XLH is a rare X-linked dominant genetic disorder characterised by renal phosphate wasting.[1] It is the most frequent cause of inherited hypophosphatemia and the most common genetic cause of rickets.[1]
- XLH is caused by mutations of Phosphate regulating Endopeptidase X-linked (PHEX) gene (located at Xp22.1).[1] This results in excess Fibroblast Growth Factor 23 (FGF23) leading to renal phosphate wasting and suppressed circulating 1,25(OH)2D, reducing intestinal phosphate reabsorption.[2]
- The resulting chronic hypophosphataemia leads to reduced bone mineralisation and rickets/osteomalacia.[2]

Suspect XLH in PEDIATRIC patients with any of the following signs and symptoms:

"Essential" features for a presumptive diagnosis of XLH in children[1]

- ☐ Decreased growth velocity
- ☐ Short stature[a,b]
- ☐ Progressive lower limb deformities[b]
- ☐ Persistently elevated ALP levels
- ☐ Renal phosphate wasting[e] – exclude other renal reasons for phosphaturia
- ☐ Serum phosphate levels below the age-related reference range[d]
- ☐ Radiographic and/or clinical evidence of active rickets that does not heal with ≥3 months of calcium and vitamin D treatment[c]

a Disproportionate short stature in severe cases (impaired limb growth with preserved trunk growth)
b Primarily in children who have started to walk (>1–1.5 years of age)
c Radiographic and/or clinical rickets that does not heal even after 3 months of vitamin D and calcium supplementation - for APAC regions with moderate-to-high prevalence of nutritional rickets
d If clinical suspicion exists and serum phosphate levels are normal, 'fasting' serum phosphate test should be conducted
e Assessed by calculating renal tubular reabsorption of phosphate in the fasting state [TmP/GFR and %TRP] based on urinary and serum phosphate and creatinine levels). The normal TmP/GFR (mmol/L) for children (both sexes) are as follows: at birth (1.43-3.43), 3 months (1.48-3.30), 6 months (1.15-2.60), age 2-15 years (1.15-2.44)[3]

Additional criteria to support or further confirm the diagnosis of XLH in children[1]

- ☐ Abnormal (waddling) gait
- ☐ Bone pain
- ☐ Rachitic rosary, Harrison's groove
- ☐ Recurrent dental abscess
- ☐ Abnormal head shape with frontal bossing
- ☐ Craniosynostosis, Chiari type 1 malformation
- ☐ Normal serum calcium, normal or mildly elevated PTH, normal 25-hydroxy vitamin D, low or inappropriately normal 1,25-dihydroxy vitamin D, elevated or inappropriately normal FGF23
- ☐ Positive family history of XLH and/or detection of pathogenic PHEX gene mutations

Abbreviations: ALP, Alkaline phosphatase; **APAC,** Asia Pacific; **TmP/GFR,** The ratio of the maximum rate of tubular phosphate reabsorption (TmP) to the glomerular filtration rate (GFR); **TRP,** Tubular Reabsorption of Phosphate; **PTH,** Parathyroid hormone

- If you suspect XLH in a pediatric patient based on the above criteria, promptly refer the patient to a specialist.
- Prompt referral, diagnosis and early treatment of XLH is associated with superior clinical outcomes[4]

References: 1. Munns CF, *et al.* JBMR Plus. 2023 May 1;7(6):e10744. **2.** Carpenter TO, *et al.* J Bone Miner Res. 2011;26(7):1381-1388. **3.** Payne RB. Ann Clin Biochem. 1998;35:201–6. **4.** Haffner D, *et al.* Nat Rev Nephrol. 2019;15:435-55.

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