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X-linked hypophosphataemia

CLINICAL REVIEW

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X-linked hypophosphataemia is a rare genetic disorder that causes renal phosphate wasting, impaired mineralisation of teeth and bones, skeletal deformities and limited mobility, all of which significantly impact on health and quality of life. This clinical review examines the recommendations for diagnosing, treating and monitoring adults with the condition.

X-linked hypophosphataemia (XLH) is a rare genetic disorder in which renal phosphate wasting leads to rickets in children and osteomalacia in adults. The condition causes skeletal deformities, reduced mobility, dental complications,

hyperparathyroidism, nephrocalcinosis and impaired kidney function (1), and significantly impacts on health, employment and quality of life (2). Patients are monitored by endocrinologists and nephrologists, as well as primary care providers and specialised orthopaedic units. Most children receive specialist follow-up until age 18, but there are no standardised recommendations for adult care in Norway. This clinical review summarises the diagnosis, treatment and follow-up of patients with XLH, based on recent literature and clinical experience.

Epidemiology and pathogenesis

XLH is caused by variants in the *phosphate-regulating endopeptidase, X-linked (PHEX) gene,* and is an inherited X-linked dominant condition (3). The prevalence is reported to be 1–9 per 100,000 (4). An ongoing registry study (5) estimates that 150–200 individuals in Norway have the condition, which is higher than previous estimates (6). Approximately 30 % of cases are due to de novo mutations (7). The pathogenic gene variants lead to an increased concentration of fibroblast growth factor 23 (FGF23), which reduces phosphate reabsorption in the kidneys, resulting in chronic hypophosphataemia (Figure 1).

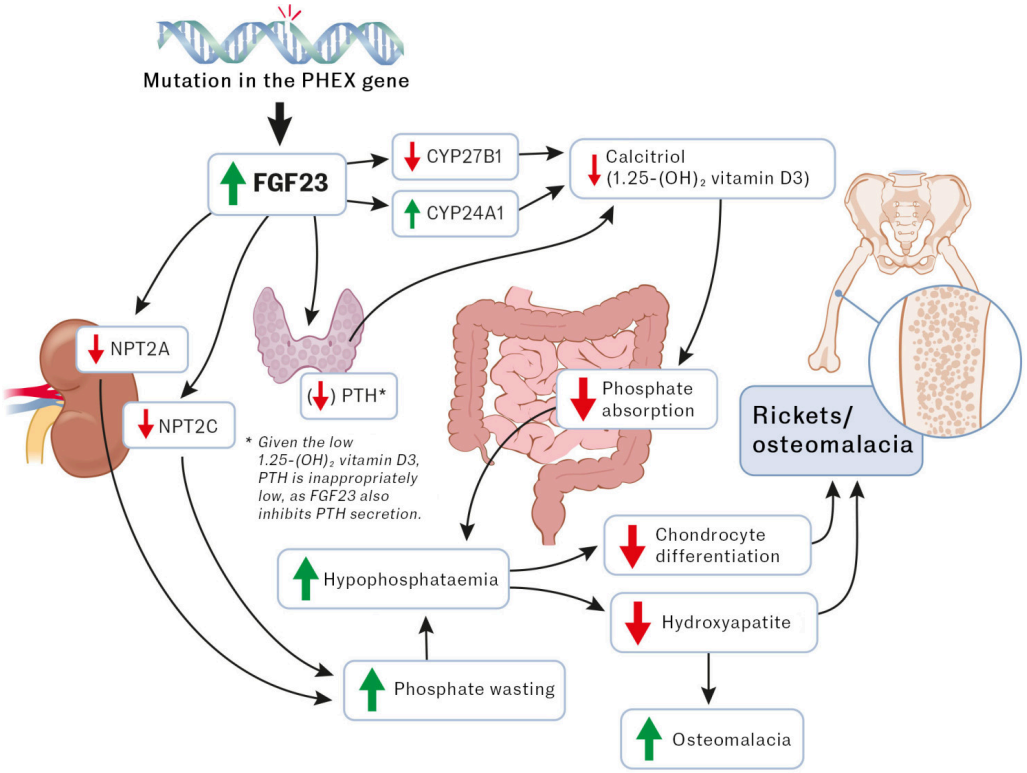

Figure 1 Pathogenesis of X-linked hypophosphatemia: mutations in the *PHEX* gene lead to elevated FGF23. This results in the downregulation of sodium/phosphate cotransporters (NPT2A and NPT2C) in the renal tubules, causing increased excretion of sodium phosphate in the urine and hypophosphataemia. FGF23 inhibits 1α-hydroxylase (CYP27B1), reducing the synthesis of 1.25-(OH)2 vitamin D while simultaneously increasing 24-hydroxylase activity (CYP27A1). This leads to reduced phosphate absorption from the intestine. A low level of 1.25-(OH)2 vitamin D does not necessarily cause hyperparathyroidism, as FGF23 also inhibits PTH secretion (8).

Hypophosphataemia and low 1.25-(OH)2 vitamin D levels impair the formation of hydroxyapatite crystals, leading to apoptosis of hypertrophic chondrocytes and, consequently, rickets and osteomalacia.

An elevated level of FGF23 also reduces the synthesis of active vitamin D (1.25-$(OH)_2$ vitamin D). Phosphate wasting and reduced levels of 1.25-$(OH)_2$ vitamin D lead to the development of rickets with misalignment in the lower limbs, such as genu valgum, insufficient mineralisation of the teeth and disproportionate short stature (6, 8).

Clinical findings

People with XLH typically develop symptoms in the first or second year of life, while in milder phenotypes, symptoms tend to appear later in life (Figure 2). The symptom burden is relatively similar for men and women (9). In children, the first symptoms include delayed motor development and reduced growth (7). Dental complications due to reduced dentin mineralisation appear in childhood (10). In adults, rickets and lack of skeletal development lead to short stature and lower limb deformities. Muscle and joint pain, as well as enthesopathies (tendon insertion pain), are common. If left untreated, osteomalacia can also occur, which can lead to insufficiency fractures, axial changes and early osteoarthritis in the spine, hips and knees (11, 12). Poor dental health with enamel damage and dental abscesses is widespread and reduces quality of life (11, 12). A study from the United States found that three out of four untreated adults had experienced five or more spontaneous dental abscesses (13). Life expectancy is approximately eight years less than that of the general population (8, 14).

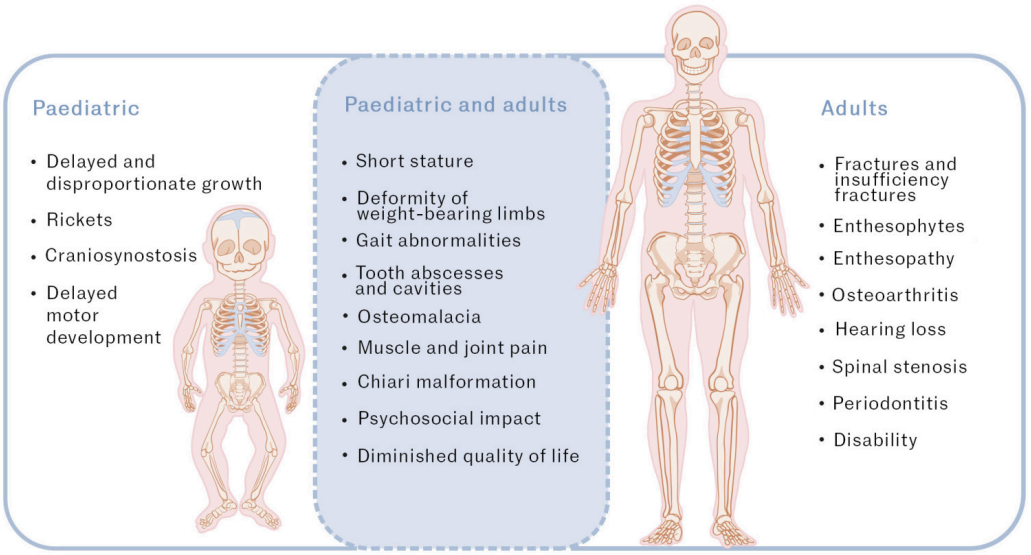

Figure 2 Clinical manifestations of X-linked hypophosphatemia (8)

Diagnosis

Most cases are diagnosed in childhood following the onset of symptoms. An overall assessment must be made of initial laboratory findings. Findings that support the diagnosis include hypophosphataemia and elevated phosphate excretion in the urine. Renal phosphate wasting is calculated based on the ratio between the renal tubular maximum reabsorption rate of phosphate and the glomerular filtration rate (TmP/GFR). Elevated serum alkaline phosphatase levels raise suspicion of rickets, while high FGF23 levels suggest PHEX mutations as the underlying cause (15, 16). FGF23 analysis is not routine but can be performed at the Hormone Laboratory at Oslo University Hospital. FGF23 levels are not necessarily elevated but inadequately suppressed relative to phosphate levels. 1.25-$(OH)_2$ vitamin D is reduced in untreated patients, and PTH is usually in the upper normal range (17). Genetic testing is recommended to confirm the diagnosis (9) but is not necessary with typical biochemical findings in the patient and their family members. De novo mutations and somatic mosaics can complicate a genetic investigation (9).

Treatment

The goal of treatment is to limit the development of rickets and osteomalacia (7). Conventional treatment is primarily recommended for children who are still growing and adults with pronounced symptoms, and includes phosphate and active vitamin D supplementation. Early treatment prevents severe lower limb deformities and enables better functional levels. The need for frequent dosing of phosphate and the strong aftertaste of the medication can reduce adherence (7).

Phosphate supplementation and active vitamin D increase calcium excretion in the urine, which increases the risk of nephrocalcinosis. This side effect has been reported in 30–70 % of patients (6). It appears to be reversible, as nephrocalcinosis is more commonly seen in children who are regularly treated with phosphate and active vitamin D, compared to adults who receive less frequent treatment (18). Monitoring PTH and calcium levels is important for limiting calciuria. Treatment with hydrochlorothiazide can, if necessary, reduce calciuria in XLH.

Prolonged elevated FGF23 levels and phosphate supplementation without the addition of active vitamin D can lead to secondary hyperparathyroidism, which exacerbates phosphaturia. Conversely, excessive supplementation of active vitamin D and/or insufficient oral phosphate intake can induce hypoparathyroidism, which inhibits bone turnover and delays the healing of osteomalacia. The goal is to maintain normal PTH levels. Secondary and tertiary hyperparathyroidism are observed in up to 80 % of adults with XLH

(19). Despite close monitoring, some patients develop impaired kidney function. Not all the mechanisms are known, but conventional treatment is believed to be a contributing factor (7).

An alternative to conventional treatment is burosumab, a monoclonal antibody that neutralises FGF23. This medication can normalise phosphate levels and promote growth (20). In 2018, the European Medicines Agency granted a conditional marketing authorisation for burosumab for the treatment of adolescents and children aged ≥ 1 year, as well as adults with radiographic evidence of osteomalacia (21). In Norway, the treatment is available for children (1–18 years) with insufficient response to conventional treatment (22). Whether burosumab can improve long-term quality of life by reducing the need for complex surgical procedures, such as valgus deformity corrections, is not clear (23). Norway is participating in a large international registry study of the long-term effects of burosumab (5).

Follow-up and long-term treatment

Even with treatment, persistent symptoms and complications are common, highlighting the need for regular multidisciplinary follow-up to ensure effective management (7). According to international recommendations, adults should have 1–2 check-ups per year with a specialist who is knowledgeable about and interested in the condition, typically an endocrinologist or nephrologist (7). Functional testing, such as the six-minute walk test, is recommended to assess functional capacity and treatment efficacy. Recommended blood tests include 25(OH)D, alkaline phosphatase, calcium, phosphate, PTH, creatinine and eGFR. Additionally, calcium, phosphate and creatinine levels in urine should be measured. Patients taking burosumab require more frequent monitoring of phosphate levels. In cases of hypertension, an echocardiogram is recommended to assess for myocardial hypertrophy (7). Renal ultrasound is advised for detecting nephrocalcinosis. If pain or suspected insufficiency fractures occur, imaging diagnostics should be performed.

Routine dental examinations are recommended twice a year, along with comprehensive jaw assessments using panoramic X-rays every two years. Spontaneous dental abscesses can be difficult to detect in their early stages, as they are not preceded by cavities, and MRI may improve diagnostics (24). Patients with XLH can be referred to the National Resource Centre for Oral Health in Rare Medical Conditions (TAKO Centre) for evaluation.

Patients may also require follow-up with a physiotherapist and a specialist in orthopaedics and/or physical medicine and rehabilitation (7).

Recommendations for the diagnosis and follow-up of XLH published in 2019 (7) have not been implemented in Norway. Our impression is that paediatric care at university hospitals is in line with these recommendations, while adult follow-up seems inconsistent. Standardising follow-up could ensure optimal treatment regardless of where in the country patients live. Adapting the recommendations to the patient population in Norway requires a thorough understanding of the actual disease burden. Along with a focus on up-to-date,

personalised treatment, guidelines could help improve quality of life (23). Factors such as disability benefits and routine dental check-ups impact on perceived and actual morbidity, thereby affecting healthcare needs. A Norwegian cross-sectional study is currently examining morbidity and quality of life among adults with XLH.

Based on clinical experience, our impression is that the gap between international recommendations and current clinical practice can be bridged with moderate but systematic measures. A checklist for annual check-ups, including dental follow-up and renal ultrasound, would be a good start.

The article has been peer-reviewed.

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