Congenital hypophosphatemia

Ineke Böckmann, Dieter Haffner

Department of Pediatric Kidney, Liver, Metabolic and Neurological Diseases, Hannover Medical School, Hannover, Germany

ABSTRACT

Maintenance of phosphate homeostasis is crucial for proper bone and tooth mineralization. Congenital hypophosphatemia, mainly caused by pathogenic variants in genes involved in the regulation of phosphate homeostasis, leads to increased secretion of the phosphaturic hormone fibroblast growth factor 23 (FGF23) from bone, selective genetic defects in the sodium-dependent phosphate cotransporters in the proximal tubules, or generalized proximal renal tubular dysfunction, as in renal Fanconi syndrome. X-linked hypophosphatemia (XLH) is the most common form of congenital hypophosphatemia. Symptoms typically emerge in the first two years of life and include growth delay, rickets, osteomalacia, bone pain, leg deformities, and a waddling gait. Depending on the specific cause of congenital hypophosphatemia, patients may show additional complications or be asymptomatic for many years. New insights into the role of FGF23 in the pathogenesis of XLH have opened the way for novel therapies, such as FGF23 inhibition. Diagnosis rests on clinical features and biochemical findings; in the absence of a definite non-genetic cause or positive family history and clear clinical presentation, it should be confirmed by genetic testing. This review discusses the pathophysiology, clinical manifestations, differential diagnosis, and clinical management of patients with congenital hypophosphatemia.

KEYWORDS

Congenital hypophosphatemia, X-linked hypophosphatemia, rickets, osteomalacia, fibroblast growth factor 23, *PHEX, SLC34A3, SLC34A1*

Introduction

Congenital hypophosphatemia was first described by Albright in 1937 in a child with rickets secondary to hypophosphatemia that did not respond to high-dose vitamin D therapy [1]. He therefore named this disease vitamin D-resistant rickets. Subsequently referred to as X-linked hypophosphatemia (XLH), it is the most common form of congenital hypophosphatemia [2,3].

Since Albright's initial description, numerous genetic defects have been identified that cause primary or secondary renal phosphate wasting leading to hypophosphatemia. Persistent hypophosphatemia causes rickets in growing children, and osteomalacia in children and adults, due to impaired growth plate cartilage and bone mineralization [4].

Congenital hypophosphatemia is usually caused by renal phosphate wasting or, rarely, by inadequate intestinal phosphate absorption. Renal phosphate wasting may result from genetic or acquired defects in proximal tubular reabsorption or from elevated phosphaturic hormones, such as parathyroid hormone (PTH) or fibroblast growth factor 23 (FGF23) [4,5]. Elevated FGF23 levels are primarily caused by pathogenic variants in several genes that lead to increased FGF23 secretion from bone. Increased circulating FGF23 impairs the synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and enhances its degradation, thereby reducing intestinal phosphate absorption and further aggravating hypophosphatemia.

Approximately 85% of cases can be explained by pathogenic variants in genes involved in the regulation of phosphate homeostasis [6].

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Contact

Dieter Haffner; haffner.dieter@mh-hannover.de

Department of Pediatric Kidney, Liver, Metabolic and Neurological Diseases

Hannover Medical School, Hannover, Germany

Phone: +49 511 532 3213 – Fax: +49 511 532 3911

Phosphate homeostasis

Phosphate homeostasis, maintained by the kidneys and intestine, ensures adequate bone and tooth mineralization [4]. Renal phosphate handling is mainly controlled by PTH and FGF23, which downregulate the sodium-dependent Pi cotransporters NPT2a and NPT2c in the proximal tubules in response to high phosphate loads. Unlike children, who have a positive phosphate balance that allows bone modeling and appropriate growth, adults maintain phosphate homeostasis at steady state. Consequently, intestinal absorption of phosphate is higher in children, in whom up to 90% of dietary phosphate can be absorbed. Phosphate is freely filtered in the kidneys through the glomerular capillaries and mainly reabsorbed in the proximal tubules via the sodium-phosphate cotransporters NaPi-IIa (NPT2a; *SLC34A1*) and NaPi-IIc (NPT2c; *SLC34A3*) in a highly regulated manner according to the body's physiological needs [7]. Circulating FGF23 is mainly derived from bone, where it is synthesized by osteocytes and osteoblasts, with serum phosphate and $1,25(OH)_2D$ levels acting as its principal stimulators. FGF23 binds to FGF receptor 1 in complex with its co-receptor

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Klotho, resulting in downregulation of NaPi-IIa and NaPi-IIc in the proximal tubules, suppression of renal $1,25(OH)_2D$ synthesis, and increased $1,25(OH)_2D$ degradation. The net effects are decreased serum phosphate and $1,25(OH)_2D$ concentrations, which may contribute to hypocalcemia. As PTH, in contrast to FGF23, stimulates renal $1,25(OH)_2D$ synthesis, the net effect of secondarily elevated PTH is an increase in serum calcium and decrease in serum phosphate levels.

Presentation and differential diagnosis of congenital hypophosphatemia

The main clinical feature of congenital hypophosphatemia in children is rickets. During infancy, patients usually show frontal bossing with occipital flattening, growth failure, thickened wrists and ankles, bone pain, progressive leg deformities (*genu varum*), and muscle weakness resulting in a waddling gait [5]. In adulthood, they may develop pseudofractures due to osteomalacia. Depending on the specific underlying cause, additional features may be detected in patients with XLH, e.g. dolichocephaly, due to craniosynostosis, dental abscesses, periodontitis, osteoarthritis, enthesopathy, and hearing loss (Figures 1,2).

Historically, patients were treated with frequent oral doses of phosphate salts and active vitamin D, which improved rickets and osteomalacia but were associated with significant side effects such as nephrocalcinosis and secondary hyperparathyroidism [5]. It is important to note that nephrocalcinosis and nephrolithiasis may sometimes be detected in congenital hypophosphatemia even before the initiation of medical treatment. This finding strongly suggests underlying pathogenic variants in genes encoding NPT2a (*SLC34A1*) and NPT2c (*SLC34A3*), associated with infantile hypercalcemia type 2 (IH-2) and hypophosphatemic rickets with hypercalciuria (HHRH), respectively. In this case, nephrocalcinosis is related to hypercalciuria caused by high $1,25(OH)_2D$ levels as discussed below [8-11].

The main biochemical findings in patients with congenital hypophosphatemia are low serum phosphate and elevated total alkaline phosphatase activity compared with the reference ranges for age and sex [4]. The diagnostic work-up is aimed at identifying the underlying cause of hypophosphatemia. Although the terms calcipenic rickets and phosphopenic rickets do not strictly reflect the underlying pathophysiology, they are still helpful in the diagnostic work-up.

Figure 3 summarizes the diagnostic work-up in patients presenting with low serum phosphate, which may suggest a diagnosis of XLH [5]. Hypophosphatemia may be due to elevated PTH levels (calcipenic rickets), impaired intestinal phosphate absorption, or phosphopenic rickets caused by renal phosphate wasting. The latter may result from inappropriately elevated FGF23 levels, genetic tubular defects, or generalized proximal tubular dysfunction (Fanconi syndrome) [4].

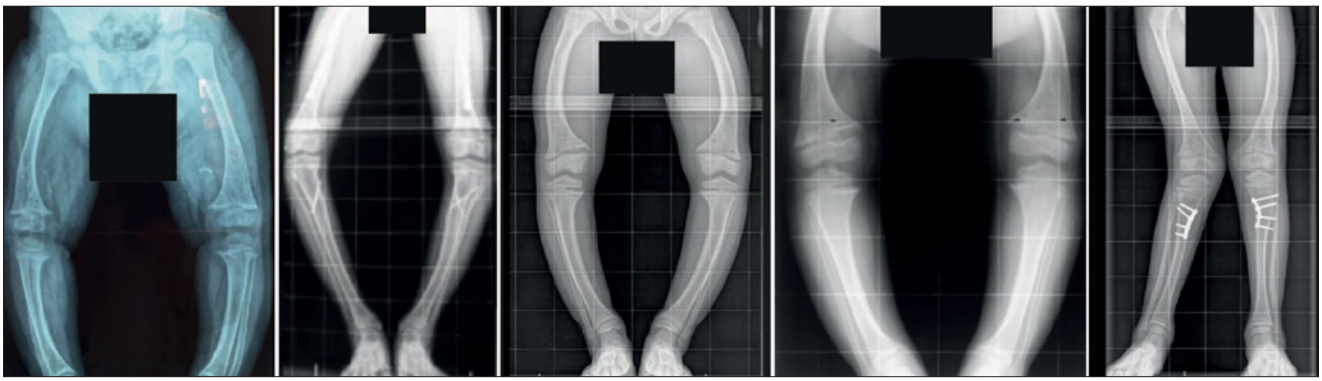
By calculating the maximum rate of renal tubular reabsorption of phosphate normalized to glomerular filtration rate (TmP/GFR), it is possible to diagnose renal phosphate wasting. This is done using the following formula: TmP/GFR = Pp – (Up x Pcr/Ucr), where Pp is plasma phosphate concentration, Up is urinary phosphate concentration, Pcr is plasma creatinine concentration, and Ucr is urinary creatinine concentration [12]. An online calculator is available [13]. Elevated PTH levels are present in calcipenic rickets, while PTH levels are usually low or even suppressed in patients with phosphopenic rickets. Low urinary phosphate concentrations suggest inadequate phosphate uptake, while inappropriately "normal" or even elevated FGF23 levels in the presence of hypophosphatemia indicate FGF23-driven causes of renal phosphate wasting [5]. Elevated circulating $1,25(OH)_2D$ levels and/or hypercalciuria suggest a diagnosis of HHRH/IH-2. Low serum bicarbonate levels and/or increased urinary concentrations of glucose, potassium, sodium, amino acids, and/or alpha-1 microglobulins point to a diagnosis of Fanconi syndrome, which is often caused by infantile nephropathic cystinosis [14]. The major causes and management of congenital hypophosphatemia are discussed below. Diagnosis should always be confirmed by genetic testing unless a non-genetic cause can be proven or the patient has a positive family history and clear clinical symptoms [4,5].

Hypophosphatemia due to increased FGF23 activity

X-linked hypophosphatemia (PHEX mutation)

X-linked hypophosphatemia (XLH) is caused by pathogenic variants in the phosphate-regulating endopeptidase homolog

Figure 1 Radiographs of the lower extremities of children with X-linked hypophosphatemia. The patients show disproportionate short stature with genu varum (bowed legs). The radiographs reveal severe leg bowing, partial fraying and irregularity of the distal femoral and proximal tibial growth plates. Note the lack of bone resorption features. (Reproduced with permission from Ref. 5).



X-linked (*PHEX*) gene. It is the most common genetic cause of congenital hypophosphatemia with a prevalence of 1.3 to 4.8 cases per 100,000 individuals [3]. *PHEX* is mainly expressed in osteocytes, osteoblasts, odontoblasts, and cementoblasts, and PHEX malfunction results in a complex metabolic bone disease and dental abnormalities ((Figures 1 and 2) [5], as well as increased FGF23 secretion from bone through mechanisms that remain poorly understood, leading to circulating FGF23 levels that are inappropriately "normal" or even elevated in the setting of hypophosphatemia. FGF23 excess causes renal phosphate wasting and reduced synthesis of $1,25(OH)_2D$, and eventually hypophosphatemia, rickets (children), and osteomalacia. Despite this clear pathogenesis of XLH-associated rickets and osteomalacia, the pathogenesis of other features such as osteoarthritis and enthesopathy is unclear. *PHEX* mutations also affect bone metabolism via various other mechanisms, e.g. accumulation of p-ASARM (Acid Serin- and Aspartate-Rich Motif) peptides and osteopontin, as well as increased expression of sclerostin, RUNX2, dentin matrix protein 1, and FGF receptors, which may also contribute to the bone phenotype in XLH [3,15].

ADHR (FGF23 mutation)

Autosomal dominant hypophosphatemic rickets (ADHR) is caused by activating pathogenic variants in the *FGF23* gene that result in impaired proteoloytic cleavage of the altered FGF23 protein, leading to elevated levels of biologically active FGF23 and renal phosphate wasting [16]. It shares many features with XLH. However, patients may be asymptomatic for many years and usually present after the first decade of life. Disease onset is often triggered by iron deficiency, which stimulates FGF23 transcription and thereby increases serum FGF23 levels [17].

ARHR (1, DMP1 mutation; 2, ENPP1 mutation)

Autosomal recessive hypophosphatemic rickets can be caused by pathogenic variants in either the *DMP1* gene, which encodes for acidic dentin matrix phosphoprotein 1 (ARHR1), or the *ENPP1* gene (ARHR2), which encodes for ectonucleotide pyrophosphatase/phosphodiesterase 1 (ARHR2) [18,19]. The clinical presentation is similar to that seen in patients with XLH. It remains unclear how mutations in *DMP1* and *ENPP1* lead to increased skeletal FGF23 production in humans. In mice, DMP1 acts as a negative regulator of FGF23 expression in osteocytes and suppresses *FGF23* gene transcription [20,21]. Other mouse studies show that *ENPP1* negatively regulates FGF23 synthesis and secretion by increasing extracellular inorganic pyrophosphate production [22,23].

Raine syndrome (FAM20C mutation)

Raine syndrome is an ultrarare disease caused by pathogenic variants in the *FAM20C* gene. Most patients die in early life due to respiratory failure [24]. Mutant FAM20C protein impairs phosphorylation of FGF23, leading to impaired FGF23 cleavage, increased circulating FGF23, hypophosphatemia, and rickets.

Figure 2 Oral manifestations of X-linked hypophosphatemia. A. Oral clinical view of a 5-year-old male patient with XLH showing a spontaneous dental abscess on the right maxillary primary central incisor. The tooth shows no discoloration or carious lesion and the child and his mother reported no history of trauma. B. Maxillo-facial cellulitis due to spontaneous necrosis of the left maxillary primary canine in the same patient at the age of 7 years. C. Panoramic radiograph of the same patient at the age of 8 years showing mixed dentition with characteristic dental features of XLH, including a normal (slightly thin) enamel layer, a radiolucent dentin layer with enlarged pulp chambers, and prominent pulp horns on both primary and permanent teeth. D. Oral clinical view of a 49-year-old woman with XLH who was diagnosed at the age of 4 years. The patient was treated with oral phosphate supplements and active vitamin D during growth for 12 years before the treatment was stopped at the age of 16 years. This treatment was resumed for 4 years from the age of 40 years before being replaced with burosumab, which had been taken for 5 years. E. Panoramic radiograph of the same patient showing generalized horizontal alveolar bone loss and teeth treated endodontically due to dental infections. (Reproduced with permission from Ref. 5).

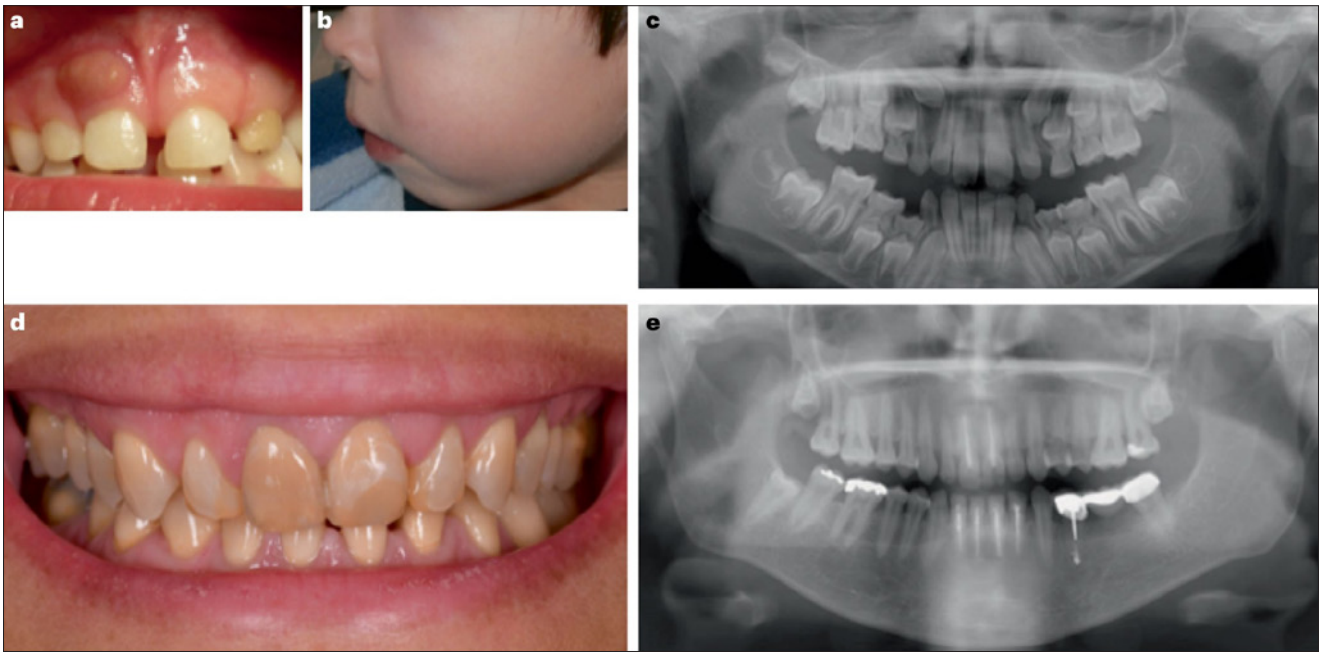
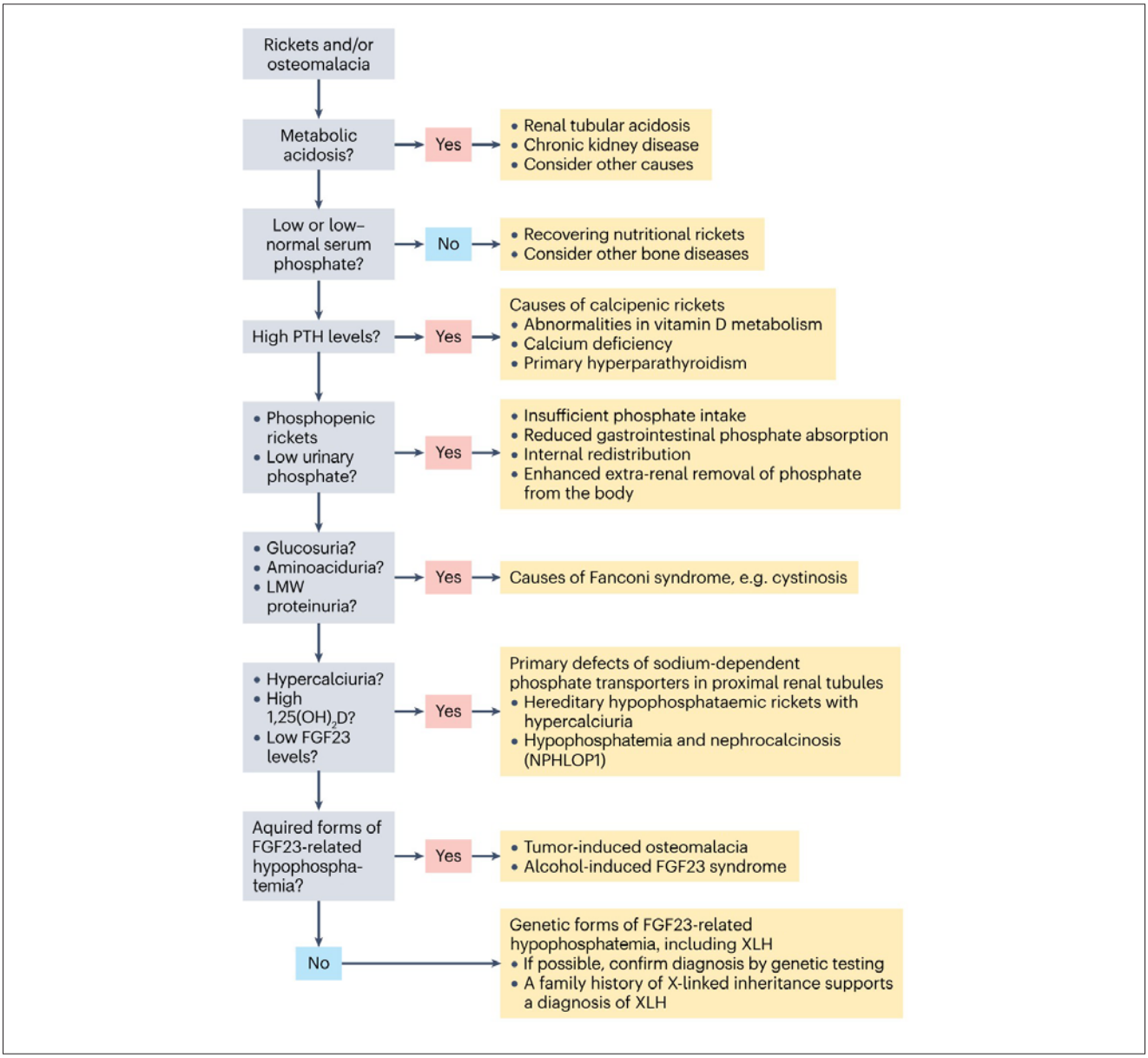


Figure 3 Algorithm for the diagnosis of X-linked hypophosphatemia (XLH). Patients usually present with rickets or osteomalacia and concomitant hypophosphatemia. The differential diagnosis is based on the mechanisms leading to hypophosphatemia, namely, high parathyroid hormone (PTH) activity (leading to calcipenic rickets or osteomalacia) and inadequate phosphate absorption from the gut or renal phosphate wasting (leading to phosphopenic rickets or osteomalacia). A family history of X-linked inheritance with full penetrance in female carriers strongly supports the diagnosis of XLH, which can be confirmed by genetic testing. FGF23, fibroblast growth factor 23; LMW, low molecular weight. (Reproduced with permission from Ref. 5).



Fibrous dysplasia and McCune-Albright syndrome

Patients with fibrous dysplasia (FD) show single or multiple fibrous skeletal lesions and localized mineralization defects on X-rays. The combination of FD with other manifestations such as café-au-lait spots, precocious puberty, and thyrotoxicosis is called McCune-Albright syndrome (MAS). Both FD and MAS are caused by gain-of-function pathogenic variants in *GNAS1* resulting in increased FGF23 secretion from bone lesions through mechanisms that remain, as yet, unknown [25].

Cutaneous skeletal hypophosphatemia syndrome

Rare cutaneous disorders caused by pathogenic variants in *HRAS*, *NRAS*, or *KRAS* result in increased FGF23 secretion, leading to hypophosphatemia [26].

Hypophosphatemic disorders with normal or suppressed FGF23 activity

HHRH (SLC34A3 mutation)

Hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive disorder caused by pathogenic variants in the *SLC34A3* gene encoding tubular NPT2c, resulting in renal phosphate wasting and leading to rickets (in children) and osteomalacia [8-10]. As hypophosphatemia suppresses FGF23 synthesis in bone, patients show high-normal or even elevated $1,25(OH)_2D$ levels. This leads to suppressed PTH levels, hypercalciuria with nephrocalcinosis, and/or kidney stones in the vast majority of patients, and sometimes hypercalcemia. Although patients usually become symptomatic in childhood, some may

remain asymptomatic for decades and only manifest symptoms related to kidney stones/nephrocalcinosis in adulthood.

IH Type 2 (SLC34A1 mutation)

Infantile hypercalcemia type 2 (IH-2) is a rare autosomal-recessive disorder caused by pathogenic variants in *SLC34A1* encoding NPT2a and manifesting in infancy. Symptoms are related to hypercalcemia and nephrocalcinosis/kidney stones, i.e. vomiting, polyuria, failure to thrive, and occasionally rickets due to concomitant hypophosphatemia [10,11]. The pathophysiology and biochemical abnormalities are similar to those seen in HHRH, but patients are more prone to hypercalcemia and less prone to rickets.

Fanconi syndrome

Fanconi syndrome is characterized by generalized proximal tubular dysfunction resulting in increased excretion of substances including water, phosphate, glucose, bicarbonate, amino acids, and low molecular weight proteins [27]. The clinical consequences are failure to thrive, polyuria, hypophosphatemic rickets, and osteomalacia. The most common cause of Fanconi syndrome is infantile nephropathic cystinosis, which is an autosomal recessive disease caused by pathogenic variants in the *CTNS* gene.

Treatment of XLH

Burosumab, a monoclonal antibody targeting FGF23, is the treatment of choice for children with XLH, as it has been shown to be superior to conventional treatment with oral phosphate salts and active vitamin D in improving rickets, growth, and physical functioning, and shows an acceptable safety profile and absence of severe side effects [5]. Sustained improvement in leg alignment can be expected for at least 3 years following initiation of this treatment in children with XLH; therefore, postponement of surgery should be considered in these patients. Adults with XLH should be treated with burosumab if they present with severe complications like pseudofractures, are not showing a sufficient clinical response to the treatment with phosphate and active vitamin D, or in the event of significant side effects. A European guideline for the diagnosis and management of children and adults with XLH was recently updated [5,28]. Figure 4 shows the key changes compared with the previous guideline.

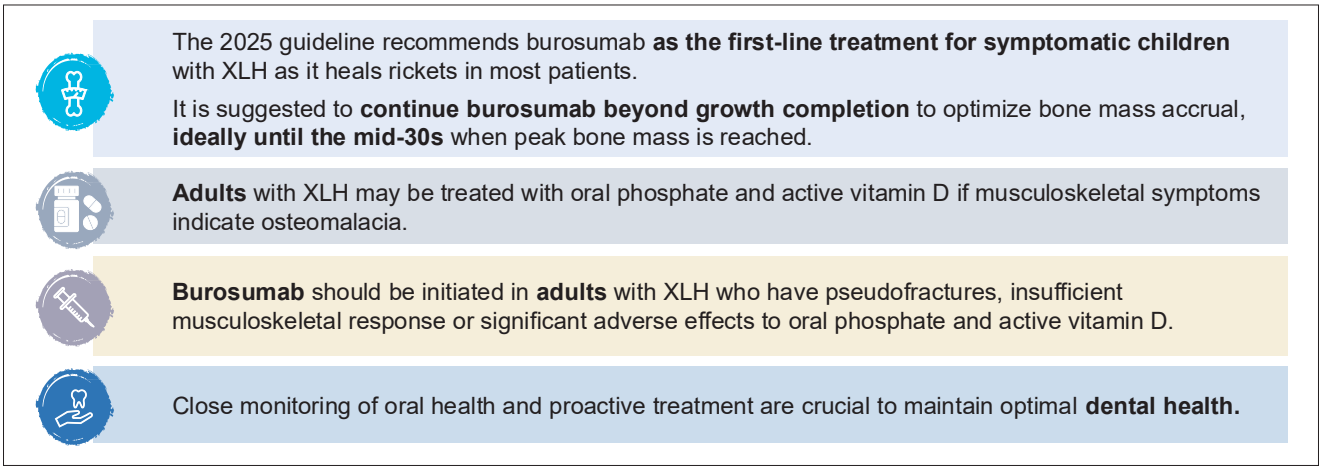
Treatment of other forms of congenital hypophosphatemia

With the exception of HHRH and IH-2, other inherited FGF23-driven causes of hypophosphatemia, e.g. ADHR and ARHR1, can generally be treated with active vitamin D and oral phosphate [29]. However, ARHR2 may be associated with arterial calcifications, which precludes treatment with active vitamin D [19]. In patients with ADHR, iron deficiency should be corrected first [17]. To date, burosumab has been approved only for the treatment of XLH and tumor-induced osteomalacia (TIO), an acquired form of hypophosphatemia. However, there are case reports indicating healing of rickets in patients with FD/MAS and cutaneous skeletal hypophosphatemia syndrome [30-32]. Patients with genetic defects of the sodium-phosphate transporters (HHRH, IH-2) are treated with phosphate only, as treatment with active vitamin D will aggravate nephrocalcinosis and/or kidney stones and hypercalcemia in these patients [9,10]. Patients with Fanconi syndrome require vigorous symptomatic treatment to compensate for excessive urinary losses. Finally, specific treatment is available for certain underlying conditions such as infantile nephropathic cystinosis [27].

Adult manifestations and long-term complications

Early treatment of congenital hypophosphatemia is crucial to prevent long-term complications. Chronic hypophosphatemia impairs bone mineralization, leading to osteomalacia, osteopenia, and pseudofractures in adulthood. Adults with XLH commonly experience bone and joint pain and are prone to develop osteoarthritis, enthesopathies, spinal stenosis, hearing loss, and arterial hypertension [5]. Some forms of congenital hypophos-

Figure 4 Key recommendations given in the updated XLH guideline [5]. (Reproduced with permission from Ref. 5).



phatemia may also lead to nephrocalcinosis, chronic kidney disease, and renal tubular dysfunction, particularly in syndromic or generalized tubulopathies such as Fanconi syndrome [27].

Summary and conclusion

Maintenance of phosphate homeostasis is essential for proper bone and tooth mineralization. Congenital hypophosphatemia is primarily caused by pathogenic variants in genes, leading to elevated FGF23 levels, selective defects of the sodium-dependent phosphate cotransporters (NaPi-IIa/IIc) in the proximal tubules, or generalized proximal tubular dysfunction. Accurate genetic diagnosis is crucial for initiating early and targeted treatment.

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