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Communication

Presentation and Diagnosis of Pediatric X-Linked Hypophosphatemia

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Abstract: X-linked hypophosphatemia (XLH) is a rare type of hereditary hypophosphatemic rickets. Patients with XLH have various symptoms that lower their QOL as defined by HAQ, RAPID3, SF36-PCS, and SF36-MCS in adult patients and SF-10 and PDCOI in pediatric patients. Early diagnosis and treatment are needed to reduce the burden, but the condition is often diagnosed late in childhood. The present review aims to summarize the symptoms, radiological and biological characteristics, and long-term prognosis of pediatric XLH. Typical symptoms of XLH are lower leg deformities (age six months or later), growth impairment (first year of life or later), and delayed gross motor development with progressive lower limb deformities (second year of life or later). Other symptoms include dental abscess, bone pain, hearing impairment, and Chiari type 1 malformation. Critical, radiological findings of rickets are metaphyseal widening, cupping, and fraying, which tend to occur in the load-bearing bones. The Rickets Severity Score, validated for XLH, is useful for assessing the severity of rickets. The biochemical features of XLH include elevated FGF23, hypophosphatemia, low 1,25(OH)2D, and elevated urine phosphate. Renal phosphate wasting can be assessed using the tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR), which yields low values in patients with XLH. XLH should be diagnosed early because the multisystem symptoms often worsen over time. The present review aims to help physicians diagnose XLH at an early stage.

Keywords: X-linked hypophosphatemia; PHEX; QOL; lower leg deformities; growth impairment; TmP/GFR; FGF23; Rickets Severity Score

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1. Introduction

X-linked hypophosphatemia (XLH) is a rare form of renal phosphate wasting and the most common type of hereditary hypophosphatemic rickets [1,2]. Its prevalence is estimated to be 1.7 per 100,000 in Norway and 5.0 per 100,000 in Japan [3,4]. These numbers are similar to those in North America, suggesting that there is little racial difference in the prevalence of this disease [4,5]. XLH is caused by a variant of the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, which regulates the expression of fibroblast growth factor 23 (FGF23) [6]. However, it remains unclear how *PHEX* mutations cause FGF23 elevation [2], which leads to phosphate wasting from the proximal tubule and decreased intestinal phosphate absorption owing to reduced 1,25-hydroxyvitamin D [1,25(OH)2D] [7]. The low phosphate level gives rise to various symptoms, such as short stature, wrist enlargement, bowed legs, frontal bossing, and dental abscess [8].

The conventional therapy of oral vitamin D and phosphate is normally used to treat short stature, one of the most common symptoms of hereditary XLH [9]. The mean final/adult height in Danish patients with XLH, more than 70% of whom did not receive the conventional treatment continuously, was 166.4 cm for males and 156.4 cm for females while that of the general population was 179.0 cm for males and 166.6 cm for females, indicating that patients with XLH can have a final height 10 cm lower than that of the general

population [10]. Another study reported that the standard deviation score (SDS) of final height in patients with XLH receiving oral vitamin D and phosphate was −2.8 [11]. Yet another study demonstrated that the SDS of height in patients receiving the conventional treatment was −2.38 ± 0.88 at diagnosis and −1.69 ± 1.11 at the final/adult height [12].

As with short stature, reduced quality of life (QOL) is a major problem for patients with XLH. Several reports demonstrated that adults with XLH had a lower QOL than the general population [13,14]. A previous study reported that 55.8%, 76.9%, 50%, and 50% of adult patients with XLH had a low QOL on the Health Assessment Questionnaire (HAQ), Routine Assessment of Patient Index 3 (RAPID3), Short Form 36-Physical Component Score (SF36-PCS), and Short Form 36-Mental Component Score (SF36-MCS), respectively [14]. Dental defects and enthesopathies were associated with poor QOL on HAQ and RAPID3 [14]. Treatment with oral vitamin D and phosphate improved the SF36-MCS score [14].

Low QOL was also reported in children with the disease [15]. Health-related QOL as defined by the SF-10 Physical Health Summary score in children with XLH was nearly 1.5 SDs below the score of 50 reported for the general population in the US [15]. Similarly, Pediatrics Outcomes Data Collection Instrument (PODCI) scores for the transfers/basic mobility, sports/physical function, and pain/comfort domains in children with XLH were 1 to 2 SDs below those of the general population in the US [15].

Early diagnosis and treatment with oral vitamin D and phosphate are needed to reduce the burden on patients with XLH. Early diagnosis is necessary to enable early treatment, which can improve the final height, biochemical parameters, radiographic outcome, and dental health of patients [16–18]. A previous study reported that the median (interquartile range) z-score for height after treatment was higher in patients who began treatment before one year old than in those who began treatment later (−0.7 [−1.5, 0.3], −2.0 [−2.3, −1.0], $p = 0.009$) [19]. Another study divided 17 patients with XLH into two groups based on their age at treatment onset (group 1: <1.0 years old; group 2: >1.0 years old) and demonstrated that the radiographic score at treatment onset, at the end of the first treatment year, and at prepuberty was higher in group 2 [17]. Another study demonstrated that the mean number of teeth in adulthood was higher in patients treated continuously during childhood than those treated after the age of five years [18]. To the best of our knowledge, there are no reports of early treatment improving future QOL in patients with XLH, but this outcome is likely, considering that dental complications, which negatively affect QOL, can be improved by early treatment [14].

Burosumab, an anti-FGF23 antibody recently introduced as a treatment for XLH [20], was shown to improve patient-reported outcomes in children with XLH, which were assessed using the Brief Pain Inventory (BPI) Worst Pain Score and the full Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score [20]. However, its efficacy, like that of the other treatments, may depends on early initiation [21].

XLH is diagnosed in childhood on the basis of a family history, symptoms, radiological findings, laboratory findings, and genetic analysis. A previous study reported that XLH is readily diagnosed in most patients with a family history of the disease [17]. Similarly, the condition may be readily diagnosed in the presence of severe symptoms, even without a family history. In contrast, the disease is more challenging to diagnose in patients with no family history and only mild symptoms. A survey of experts in Italy demonstrated that 16% of patients with XLH received their diagnosis at the age of 12 years or older [9]. Another study reported that the mean age at diagnosis in children with XLH stemming from a de novo *PHEX* mutation was 3.9 ± 3.1 years (range: 0.9–13.1 years) [22]. Diagnosis may be further delayed in developing countries where vitamin D deficiency is common [7].

To diagnose XLH early, it is important that pediatricians and orthopedic surgeons be familiar with the characteristics of this disease. While several recent reviews have summarized the clinical characteristics of XLH [1,6,7,22–24], only a few reports have discussed the frequency and timing of the symptoms. The present review aims to summarize the symp-

toms of pediatric XLH by focusing on their frequency, timing, and related radiological and biological findings.

2. Clinical Features

Patients with XLH have a variety of symptoms associated with low serum phosphate. The clinician should be aware of the typical age at the onset of each symptom and its frequency. Table 1 summarizes the timing of XLH symptoms.

Table 1. Clinical features for diagnosing XLH presented in recent reviews.

Age	Clinical Features	Haffner, 2019 [23]	Lambert, 2019 [24]	Rothenbuhler, 2020 [22]	Juraibah, 2021 [7]	Laurent, 2021 [1]	Baroncelli, 2021 [6]
From age 6 months to 1 year	Lower leg deformities	○	○ ‡	○ ‡	○ ‡	○ ‡	○ ‡
	Craniosynostosis	○	○ ‡	○ ‡	○ ‡	○ ‡	○
	Growth impairment †	○ ‡	○ ‡	○ ‡	○ ‡	○ ¶	○ ‡
From age 1 year to 2 years	Waddling gait	○	○ ‡	○ ‡	○ ‡	○ ‡	○ ‡
	Progressive lower limb deformities	○	○ §	ND	ND	ND	○ ‡
	Delayed gross motor development	○	○ ‡	○ ‡	○ ‡	ND	○ ‡
	Delayed standing	ND	ND	○ ‡	ND	ND	ND
	Delayed walking	○	○ ‡	○ ‡	ND	ND	○ ‡
	Torsional components	○	ND	ND	○ ‡	ND	ND
	Widening of the distal metaphysis at the wrists and ankles	○	○ ‡	○ ‡	○ ‡	ND	○ ‡
Age 3 years or older	Dental abscess	○	○ ‡	○ ‡	○ ‡	○ ‡	○ ‡
	Dental malposition	ND	ND	ND	ND	ND	○ ‡
Older children	Bone pain	○	○ ‡	○ ‡	○ ‡	○	○ ‡
	Hearing loss	○	○ ‡	○ ‡	○ ‡	○‡	○

Abbreviations: XLH, X-linked hypophosphatemia; ND, not described. † Also appears at later ages. ‡ No mention of when they appeared. § Varus deformity develops in younger children, and valgus deformity develops in children approaching puberty. ¶ Growth impairment becomes evident from 9 to 12 months of age.

Lower leg deformities begin to materialize as early as six months of age [23]. However, many parents of patients become aware of the symptoms as these deteriorate when the patient begins walking [23]. A previous study reported that most patients (94.8%) had leg deformities, which were severe, moderate, and mild in 28%, 47%, and 25% of the cohort, respectively [9]. Delayed tooth emergence and premature craniosynostosis may begin at this age or a little later [6]. The latter symptom, which was found to occur in 60% of children with XLH, is usually caused by abnormal fusion of the sagittal suture and results in a dolichocephalic head conformation [23,25]. Because both these symptoms also occur in other diseases, diagnosing XLH on the basis of these symptoms alone is challenging, and careful monitoring and testing are necessary in children who have them.

Growth impairment is another major symptom of pediatric XLH. Children with XLH are of average height at birth and begin to exhibit growth impairment during the first year of life [17,26]. A survey of 175 Italian patients found stature lower than −2 SD in 67% of patients with XLH [9]. One study reported that growth of the legs was uncoupled from that of the trunk, with the leg length SDS decreasing progressively during childhood and adolescence while sitting height SDS increased during late childhood [27].

Delayed gross motor development, waddling gait, and progressive lower limb deformities become apparent during the second year of life [6,23]. Blood tests and X-rays should be performed if patients present with any of these symptoms. In addition to delayed gross motor development, such as delayed standing or walking, XLH patients have weaker muscle strength than controls [28]. One researcher mechanographically compared the muscle

force of thirty XLH patients to that of age- and gender-matched controls and found that muscle strength was significantly weaker in the former [28]. Torsional components and distal metaphyseal widening in the wrists and ankles were also documented at a similar age [23].

Dental abscesses, especially in the canine teeth, are highly prevalent in patients aged >3 years [23,29]. Approximately one third of patients with XLH have at least one dental abscess [9]. Poor mineralization leading to dentin defects is one of the causes of these abscesses [6]. Other dental symptoms, such as dental malposition, are also observed [9].

Bone pain, which becomes more prevalent with age, is also a common symptom [1,9]. Data from pediatric hospitals in Italy demonstrated that two thirds of patients with XLH experienced bone pain [9]. A study in East Asia demonstrated the frequency of patients with XLH with bone pain to be 5/14 (35.7%) among children and 19/32 (59.4%) among adults [30].

Bone pain in young adults is classified into spontaneous fracture-related and osteomalacia-related types [2,23]. Fractures occur in the femur or tibia and usually present as localized pain [2]. Osteomalacia-related bone pain, the mechanism of which is unknown, should be considered if fractures are absent [1,2]. Oral vitamin D and phosphate therapy improve the bone pain but are insufficient for a cure [2]. Many pediatric and young adult patients with XLH receiving conventional treatment experience bone pain, which negatively affects their QOL [14,30]. The survey in East Asia cited above demonstrated that patients with XLH had a physical component summary score of 41.2 on their 36-item Short Form health survey version 2 (SF-36v2), which was lower than the normal score of 50 [30].

Other symptoms of XLH include hearing impairment and Chiari type 1 malformation, which occurred in five and 25% of cases, respectively, in previous studies [9,31]. Most patients with Chiari type 1 malformation are asymptomatic, but central apnea and lower cranial nerve dysfunction may be present [23]. Although hearing loss is infrequent, it becomes more evident with age and therefore, hearing tests are recommended for children aged eight years or older if symptoms of hearing difficulty begin to appear [23].

A previous study described the long-term consequences of this disorder when no treatment was administered. A study of the natural history of 22 adults with XLH demonstrated that 8, 17, and 19 had bone pain, genu varum, and significant dental problems, respectively [10], indicating that patients without treatment were more likely to experience these symptoms.

3. Radiological Findings

Patients with XLH have hypophosphatemia, which in children impairs bone and growth plate mineralization or causes rickets. Critical radiological findings of rickets include metaphyseal widening, cupping, and fraying [1,7], which tend to occur in the load-bearing bones, such as the femur and tibia [32]. Radiography of the left hand, lower femur, and upper tibia is an easy, non-invasive method of detecting these findings [32,33]. Metaphyseal enlargement in these bones can be detectable on the medial side [33]. Another radiological finding of rickets is long bone deformities, such as genu varum or genu valgum [32]. Bone-within-a-bone, which is caused by differences in bone growth and the periosteal reaction and indicates new bone formation in response to abnormal stimulation, is also a crucial radiological finding of rickets [32], although it is also observed in other disorders.

X-rays are also useful for assessing the severity of rickets. The Rickets Severity Score (RSS) is based on the degree of metaphyseal fraying and concavity and the proportion of affected growth plates in the wrists, knees, and ankles [1,33]. The RSS is a ten-point scale, with a score of ten indicating the highest severity, as described in Table 2 [34]. The RSS, which has been validated for XLH [35], correlates with the serum ALP value [34,35]. In recent years, the Radiographic Global Impression of Change (RGI-C) score, a seven-point, subjective scale assessing changes between X-ray findings at two time points, has come to be used when evaluating the severity of rickets [35]. The RGI-C score correlates with the

serum phosphate, serum ALP, RSS, and comfort/pain functioning values and is considered a reliable, valid, and sensitive tool for assessing pediatric XLH [36].

Table 2. Rickets Severity Score [a] [34].

Evaluation Site	Grade or Multiplier	Radiographic Features
Radius and ulna [b]	Grade	
	0	Normal
	1	Widened growth plate, irregularity of metaphyseal margins, no concave cupping
	2	Metaphyseal concavity with fraying of margins
Femur and tibia [b]	Grade	
	0	Normal
	1	Partial lucency, smooth metaphyseal margin visible
	2	Partial lucency, smooth metaphyseal margin not visible
	3	Complete lucency, epiphysis appears widely separated from distal metaphysis
	Multiplier	
	0.5	≤1 condyle or plateau
	1	2 condyles or plateaus

[a] Rickets Severity Score = grade of radius + grade of ulna + grade of femur × Multiplier + grade of tibia × Multiplier, [b] Scored separately.

The radiological findings of osteomalacia in older children include insufficiency fractures, a coarse trabecular pattern, and Loozer zones. The latter, also known as Milkman lines or pseudofractures, are radiolucent lines composed of non-mineralized osteoid [32,37]. These findings occur in high-stress areas, such as the femoral neck and tibial shaft [32,37].

4. Biochemical Findings

The biochemical features of XLH include elevated FGF23, hypophosphatemia, low 1,25(OH)2D, and elevated urine phosphate [6] (Table 3). If XLH is suspected on the basis of a family history, clinical symptoms, or radiological findings, the patients should receive blood and urine tests.

Table 3. Summary of test findings for diagnosing XLH.

Radiologic Findings	Biochemical Findings	Genetic Findings
Widening of the metaphysis Cupping of the metaphysis Fraying of the metaphysis Enlarged metaphysis Long bone deformities Bone-within-a-bone	*Blood test* Decreased P Increased ALP Normal or increased PTH Low or normal $1,25(OH)_2D$ Increased FGF23	*Sanger sequencing* *MLPA* *Next-generation sequencing* Deletion Missense variant Nonsense variant Splicing variant Frameshift variant
	Urine test Low TmP/GFR	

Abbreviations: XLH, X-linked hypophosphatemia; P, phosphate; ALP, alkaline phosphatase; PTH, parathyroid hormone; $1,25(OH)_2D$, 1,25-hydroxyvitamin D; FGF23, fibroblast growth factor 23; TmP/GFR, tubular maximum reabsorption of phosphate per glomerular filtration rate; MLPA, multiple ligation-dependent probe amplification.

The simplest screening test for XLH involves assessing for a decreased serum phosphate concentration, increased alkaline phosphatase (ALP), normal or slightly elevated parathyroid hormone (PTH), and low or normal 1,25(OH)2D in blood [6,23]. However, there are several pitfalls. First, the serum phosphate level might be normal in the first three to four months of life [23,38]. Frequent breastfeeding may compensate for renal phosphate wasting, and several months are usually required for the phosphate level to fall below the lower limit of the age-appropriate reference value [7]. Second, the normal range of serum phosphate and ALP differ by age group. The Pathology Harmony Group (UK) demonstrated that the serum phosphate reference interval in neonates and adolescents was 1.3–2.6 mmol/L (4.0–8.1 mg/dL) and 0.9–1.8 mmol/L (2.8–5.6 mg/dL), respectively, suggest-

ing that serum phosphate decreases with age [39]. Similarly, serum ALP is high in early childhood and adolescence, when bone formation is at its height [40].

Tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR), a marker of renal phosphate wasting, was found in one study to be lower in patients with XLH than in control subjects [23]; the same was found to be the case in patients with secondary hyperparathyroidism, such as nutritional vitamin D deficiency or vitamin D-dependent rickets [7]. The serum PTH level is helpful in differentiating XLH from other conditions; for instance, it is normal or mildly elevated in XLH and high in secondary hyperparathyroidism [7]. Moreover, in patients with rickets caused by impaired dietary phosphate absorption, TmP/GFR is normal or high [7]. As with serum phosphate and ALP, the normal TmP/GFR value varies by age. Previous reports demonstrated that the mean TmP/GFR level was highest at the age of 0–6 months at approximately 1.5–1.6 μmol/mL (4.6–5.0 mg/dL) and decreased to 0.9–1.0 μmol/mL (2.8–3.1 mg/dL) by adulthood [41,42].

Last but not least, serum FGF23 is helpful in the differential diagnosis of XLH [43,44]. For example, FGF23 is a useful marker for distinguishing patients with XLH from those with vitamin D deficiency rickets [43]. However, these two conditions sometimes demonstrate similar 25-hydroxyvitamin D (25[OH]D) and PTH values. Chemiluminescent enzyme immunoassays for FGF23 are available in some developed countries [44,45].

5. Genetic Findings

Genetic testing is useful for diagnosing XLH and is often employed when clinical features, radiological findings, and biological features are insufficient for diagnosis. Furthermore, genetic testing can differentiate XLH from other forms of hypophosphatemic rickets, such as autosomal recessive hypophosphatemic rickets (ARHR). Patients with ARHR with loss-of-function mutations in *ENPP1* [46] have widespread arterial calcification in early life or symptoms associated with hypophosphatemic rickets in later life [47]. Since the clinical course and inheritance pattern of ARHR differ from those of XLH, it is important to differentiate between these two conditions.

The genetic tests most often performed are Sanger sequencing, multiple ligation-dependent probe amplification (MLPA), and next-generation sequencing [48–51]. Approximately 80–90% of clinically diagnosed XLH cases involve a *PHEX* variant [1,52,53]. Although some studies have reported a genotype–phenotype correlation in XLH [54,55], other reports have not reported this correlation [1,56]. While genetic testing is useful, it should be performed in a facility that can also provide genetic counseling.

6. Treatment

A brief summary of treatments for rickets in XLH is in order. The classical therapy for XLH is oral vitamin D and phosphate. This therapy improves short stature and QOL [11,12,14], as described in the Introduction. However, it is difficult completely to normalize the serum ALP value, Tmp/GFR, and RSS [2,57], and the treatment cannot resolve dental complications or improve the patient's QOL [57,58].

Another treatment for short stature is growth hormone (GH), which improves the height SDS of patients with XLH [11,59,60]. A previous study reported that the height SDS in patients with XLH increased from −3.5 SD to −2.4 SD after three years of GH administration [16]. Baroncelli et al. demonstrated that the final height SDS in patients with XLH receiving GH and classical therapy improved from −3.4 SD to −2.1 SD, while patients receiving conventional therapy alone failed to demonstrate an increase [11].

Burosumab, an anti-FGF23 antibody recently introduced as a treatment for XLH [20], improves biochemical markers, such as serum phosphorus, TmP/GFR, and 1, 25(OH)2D; osteoid volume/bone volume as assessed by transiliac bone biopsies; fracture healing; and RSS, RGI-C, and height Z scores [61–65]. Burosumab, which targets increased FGF23, is expected to improve various symptoms as a radical treatment, although data on the long-term outcomes are not yet available.

7. Conclusions

The present review summarized the clinical, radiological, and biochemical features and genetic analysis of patients with XLH. This multisystem disorder is rare and challenging to diagnose. However, early diagnosis is of paramount importance because the multisystem symptoms deteriorate over time, negatively impacting the patients' QOL.

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