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Delayed Diagnosis of Probable X-Linked Hypophosphatemia Revealed by a Femoral Fragility Fracture in a 33-Year-Old Man: A Case Report

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Abstract

We report the case of a 33-year-old man with short stature, lower limb deformities, and dental abnormalities since childhood, who had never received a diagnosis or specialized medical follow-up. He had sustained a femoral fracture after minor trauma at the age of 14. His mother and one of his sisters had a similar morphological appearance. He was admitted for mechanical pain in the right hip, which revealed a femoral fragility fracture. Clinical examination showed marked genu varum, bilateral tibial bowing, and multiple tooth loss. Laboratory investigations revealed severe hypophosphatemia with inappropriately preserved phosphaturia, indicating renal phosphate wasting, along with an elevated intact fibroblast growth factor 23 (FGF23) level, normal serum calcium and renal function, and elevated alkaline phosphatase. Based on these clinical, biochemical, and radiological findings, a diagnosis of probable X-linked hypophosphatemia (XLH) was made; *PHEX* gene sequencing could not be performed for financial reasons. After correction of 25-hydroxyvitamin D insufficiency, treatment with divided doses of oral phosphate and active vitamin D was initiated; however, follow-up was limited by poor treatment adherence and financial constraints. This case suggests that XLH can remain undiagnosed until adulthood and that, in adults with short stature, lower limb deformities, low-trauma fractures, and dental abnormalities, serum phosphate should be measured.

Categories: Genetics, Rheumatology, Endocrinology/Diabetes/Metabolism

Keywords: fgf23, fragility fracture, hypophosphatemic rickets, osteomalacia, phex gene, x-linked hypophosphatemia

Introduction

X-linked hypophosphatemia (XLH) is a rare genetic disorder caused by loss-of-function mutations in the *PHEX* gene, resulting in inappropriately elevated levels of fibroblast growth factor 23 (FGF23). FGF23 promotes renal phosphate wasting and inhibits the synthesis of 1,25-dihydroxyvitamin D (1,25(OH)2D), leading to impaired bone mineralization, which manifests as rickets in children and osteomalacia in adults [1,2]. With an estimated prevalence of 1 in 20,000 to 1 in 70,000 individuals, XLH is the most common cause of hereditary hypophosphatemic rickets [3]. In infants and children, the disease typically presents with rickets, growth retardation, lower limb deformities, and spontaneous dental abscesses, while craniosynostosis and Chiari type I malformation occur less frequently [2-4]. In adults, the clinical picture is dominated by persistent bone pain, early-onset osteoarthritis, pseudofractures (Looser zones), mineralizing enthesopathies, periodontitis, and tooth loss [2,5,6]. Lack of pediatric follow-up and frequent misdiagnosis as nutritional vitamin D deficiency may delay the diagnosis, sometimes until adulthood [1,7]. Conventional therapy, combining multiple daily doses of oral phosphate with active vitamin D (calcitriol or alfacalcidol), improves rickets, growth, lower limb deformities, and dental mineralization when initiated early in childhood [3,8]. However, it does not correct the underlying FGF23 excess, requires strict adherence to several daily doses, frequently causes gastrointestinal side effects, and exposes patients to nephrocalcinosis and secondary or tertiary hyperparathyroidism [3,7]. Burosumab, a fully human monoclonal antibody targeting FGF23, is the most recent targeted therapy and improves renal tubular phosphate reabsorption [9-11]. However, access to this treatment remains limited in many countries. Distinguishing XLH from nutritional rickets and other causes of hypophosphatemia remains a frequent diagnostic challenge, and a delayed diagnosis exposes patients to irreversible skeletal deformities, fractures, and dental complications. We report the case of an adult with probable XLH that remained undiagnosed throughout childhood and was revealed by a femoral fragility fracture, illustrating the late complications of the disease.

Case Presentation

A 33-year-old man from Marrakech, Morocco, a chronic smoker (one pack per day for 10 years, i.e., 10 pack-years), was admitted for mechanical pain in the right hip.

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His medical history revealed growth retardation and poor weight gain since childhood, without any specialized medical follow-up. He measured 1.52 m and weighed 64 kg (body mass index: 27.7 kg/m²). His mother and one of his sisters have a similar morphological appearance, including short stature, and neither had received an etiological diagnosis. At the age of 14, he had sustained a femoral fracture following minor trauma, retrospectively suggesting underlying bone fragility.

Clinical examination revealed lower limb deformities, with marked genu varum and bilateral tibial bowing (Figure 1). Poor oral health with loss of several teeth was also noted (Figure 2).



FIGURE 1: Lower limb deformities: genu varum and bilateral tibial bowing



FIGURE 2: Oral and dental findings: multiple tooth loss and extensive destruction of the remaining teeth

Laboratory findings are summarized in Table 1. Serum phosphate was markedly decreased, whereas 24-hour urinary phosphate excretion remained within the normal range. In an individual with normal tubular function, hypophosphatemia of this severity would be expected to cause a marked reduction in urinary phosphate excretion; this inappropriately preserved phosphaturia therefore indicated renal phosphate wasting. Similarly, the FGF23 level was elevated, whereas FGF23 secretion would normally be suppressed in response to hypophosphatemia. Serum calcium and renal function were normal, alkaline phosphatase and parathyroid hormone (PTH) were elevated, and 25-hydroxyvitamin D was in the insufficient range.

Parameter	Result	Reference range (adult)	Interpretation
Serum phosphate	18.23 mg/L (0.59 mmol/L)	25-45 mg/L (0.81-1.45 mmol/L)	Markedly decreased
Serum calcium	90.46 mg/L (2.26 mmol/L)	85-102 mg/L (2.12-2.55 mmol/L)	Normal
Alkaline phosphatase	219 IU/L	40-130 IU/L	Elevated
25-Hydroxyvitamin D	21 ng/mL	≥30 ng/mL	Insufficient
Parathyroid hormone	78 pg/mL	15-65 pg/mL	Mildly elevated
Intact FGF23	108.2 pg/mL	23.2-95.4 pg/mL	Elevated
Urea	0.3 g/L	0.15-0.45 g/L	Normal
Creatinine	6.29 mg/L (55.6 μmol/L)	7-12 mg/L (62-106 μmol/L)	Normal renal function
24-hour urinary phosphate	475 mg/24 h (15.3 mmol/24 h)	400-1300 mg/24 h	Inappropriately preserved despite hypophosphatemia

TABLE 1: Laboratory findings at admission
FGF23: fibroblast growth factor 23

Radiographs obtained to investigate the right hip pain revealed a metaphyseal fracture of the right femur that had occurred without significant trauma. Pelvic and lower limb radiographs also demonstrated the associated skeletal deformities (Figures 3-5).



FIGURE 3: Radiographs of the lower legs showing bilateral tibial bowing and a transverse cortical lucency of the left tibia (arrow), consistent with a pseudofracture



FIGURE 4: Anteroposterior pelvic radiograph showing deformity of the proximal femurs, a fracture of the right proximal femur, and a transverse cortical lucency of the left proximal femur consistent with a pseudofracture (arrows)

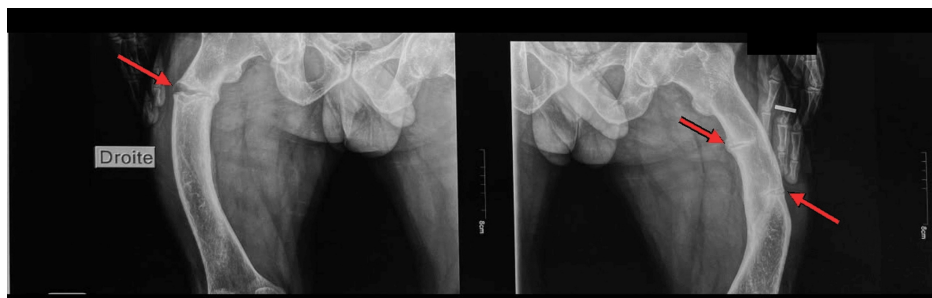


FIGURE 5: Femoral radiographs showing femoral bowing, right proximal femoral fracture, and two transverse cortical lucencies of the left femur consistent with pseudofractures (arrows)

Based on the clinical, biochemical, and radiological findings, a diagnosis of probable XLH was made. *PHEX* gene sequencing, which is not available in Morocco and is not covered by the patient's health insurance, could not be performed owing to its cost. After correction of 25-hydroxyvitamin D insufficiency, treatment was initiated with divided doses of oral phosphate (Phosphoneuros, 50 drops three times daily) and active vitamin D (alfacalcidol 0.75 µg/day). A multidisciplinary follow-up involving rheumatology, endocrinology, and dentistry was planned. However, follow-up was irregular: adherence to the multiple daily doses of phosphate was poor, and the patient's limited financial resources hindered regular consultations and laboratory monitoring. Consequently, objective clinical and biochemical outcome data could not be obtained.

Discussion

Our case illustrates a classic scenario: probable XLH that remained unrecognized for many years despite symptoms present since childhood. Short stature, genu varum, tibial bowing, a femoral fracture following minimal trauma at the age of 14, and early tooth loss nevertheless constituted a highly suggestive set of findings. The main diagnostic pitfall is confusion with nutritional rickets: in XLH, serum calcium is normal, parathyroid hormone (PTH) is normal or mildly elevated, and 25-hydroxyvitamin D is not markedly decreased, whereas hypophosphatemia is constant and persistent, and supplementation with native vitamin

D alone is ineffective [1,2,7].

When faced with chronic hypophosphatemia, the first step is to establish its renal origin. Twenty-four-hour urinary phosphate excretion, taken in isolation, is of limited interpretive value because it depends on dietary intake; the reference approach relies on calculating the tubular reabsorption of phosphate (TRP) and, above all, the maximal tubular reabsorption of phosphate normalized to the glomerular filtration rate (TmP/GFR) from paired fasting blood and urine samples [2,3,6]. In our patient, preserved phosphaturia despite profoundly low serum phosphate indicated renal phosphate wasting; calculation of TmP/GFR, which was not performed, would have strengthened this demonstration.

Measurement of FGF23 then makes it possible to distinguish FGF23-dependent hypophosphatemia from other causes. An elevated level, or one that is simply inappropriate for the degree of hypophosphatemia, points toward XLH, autosomal dominant or autosomal recessive hypophosphatemic rickets, or tumor-induced osteomalacia [12]. The latter should always be considered in adults; in this case, the onset of symptoms in childhood, the sequelae-type nature of the deformities, and the similar morphological appearance of his mother and one of his sisters favor a hereditary form. Conversely, hypophosphatemia due to proximal tubulopathy (Fanconi syndrome) is accompanied by normoglycemic glycosuria, aminoaciduria, renal tubular acidosis, and hypouricemia, without elevated FGF23 [6].

In adulthood, the disease is dominated by osteomalacia and its consequences: diffuse bone pain, pseudofractures, insufficiency fractures, mineralizing enthesopathies, early-onset osteoarthritis and, less commonly, spinal canal stenosis due to ligamentous ossification [2,5,13]. In a UK cohort of 59 adults with XLH, orthopedic surgery was common, and dental involvement (63%), nephrocalcinosis (42%), and hearing impairment (14%) were frequently reported [5]. Quality of life is significantly impaired in symptomatic patients [13]. Our patient's femoral fracture, which occurred without significant trauma, fits fully within this picture.

Radiologically, plain radiography remains central for detecting pseudofractures, enthesopathies, and deformities. Bone densitometry, by contrast, is of little diagnostic value: bone mineral density may be normal or even increased at the spine owing to enthesopathies and hyperostosis, and it does not reflect the qualitative mineralization defect characteristic of osteomalacia [3,6].

Conventional treatment in adults combines oral phosphate, divided into three to five daily doses, with active vitamin D (calcitriol or alfacalcidol) [3,8,14]. It is not recommended in asymptomatic adults but is indicated in the presence of bone pain, pseudofractures, or fractures, in the perioperative period of orthopedic surgery, and in cases of progressive dental disease [3]. Dose splitting is essential: a single high dose causes a peak in serum phosphate that stimulates PTH and FGF23 secretion, exposing the patient to secondary and then tertiary hyperparathyroidism. Monitoring relies on serum calcium, urinary calcium, PTH, and renal imaging to detect nephrocalcinosis, a classic complication of conventional therapy [3,7]. Prior correction of native vitamin D insufficiency, as in our patient, is also required. In our patient, the burden of multiple daily doses and limited financial resources resulted in poor adherence and irregular follow-up, illustrating the practical limitations of conventional therapy in resource-limited settings.

Burosumab, a fully human monoclonal antibody directed against FGF23, has changed the prognosis of the disease. In adults, it durably normalizes serum phosphate, improves histomorphometric parameters of osteomalacia on transiliac bone biopsy, promotes healing of pseudofractures, and reduces pain [10]; in children, it has proven superior to conventional therapy in terms of rickets healing and growth [9,11]. However, its cost and limited availability remain major barriers in many countries, where conventional management is still the norm.

Finally, XLH is inherited in an X-linked dominant manner: an affected man transmits the mutation to all his daughters and none of his sons, whereas an affected woman transmits it to half of her offspring regardless of sex. In our patient, the similar morphological appearance of his mother and one of his sisters is consistent with maternal transmission; however, this observation relies on the patient's report, and short stature alone does not establish X-linked inheritance. Clinical, biochemical, and ideally genetic assessment of these relatives would be required to confirm it. In a 33-year-old patient of reproductive age, this warrants genetic counseling: if XLH is confirmed, all of his daughters would inherit the mutation, whereas his sons would be unaffected. Management should be multidisciplinary and long-term [3].

This report has several limitations that affect diagnostic certainty. First, renal phosphate wasting was not quantified by TmP/GFR calculation, as paired fasting blood and urine samples were not obtained. Second, molecular confirmation is lacking: PHEX sequencing, which is not available in Morocco and must be performed abroad, could not be afforded by the patient. Third, the family history relies on the patient's report: his mother and sister were not examined, no biochemical assessment or segregation analysis was performed, and no formal pedigree could be constructed. Finally, longitudinal data on treatment response are lacking, as follow-up was limited by poor adherence and financial constraints. For these reasons, the diagnosis should be considered probable rather than confirmed, although the combination of childhood-onset deformities, renal phosphate wasting, elevated FGF23, pseudofractures, and a family history

compatible with maternal transmission strongly supports it.

Conclusions

This case describes a probable adult form of XLH that remained unrecognized until the age of 33 and was revealed by a femoral fragility fracture associated with multiple pseudofractures. In this patient, the combination of childhood-onset short stature, lower limb deformities, a previous low-trauma fracture, dental abnormalities, and a similar morphological appearance in his mother and sister was highly suggestive, and measurement of serum phosphate was the key step that led to the identification of renal phosphate wasting with elevated FGF23. Although molecular confirmation could not be obtained, this case suggests that, in adults with such a presentation, serum phosphate should be measured to avoid prolonged diagnostic delay.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Salma Zniber, Kaoutar Elaati, Zineb Baba, Ahmed Mougui, Ahlam Belkhou

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. NA issued approval NA. Ethical committee approval was not required for this single case report in accordance with the policies of the Department of Rheumatology, Mohammed VI University Hospital, Marrakech. Informed consent for treatment and for publication in an open-access journal was obtained from the patient. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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