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CASE BASED REVIEWS

# Targeting the underlying pathophysiology in X-linked hypophosphatemic rickets in adults

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## ABSTRACT

X-linked hypophosphatemic rickets (XLHR) is a life-long phosphate waste disorder that presents in early childhood with lower limb deformities, stunted growth, and bone and joint pain. In adults, osteomalacia and fractures may develop, aggravating bone and joint pain, stiffness, and disability. A 50-year-old woman with XLHR was referred to Rheumatology for incapacitating pain in her left lower limb with gait impairment. A pseudofracture was identified in the radiography of long bones, and secondary hyperparathyroidism was also observed. Treatment was optimized, and marked clinical improvement occurred. The authors review and discuss the underlying pathophysiology of this disease and its adequate management.

**Keywords:** Secondary hyperparathyroidism; Pseudofracture; X-linked hypophosphatemic rickets; Osteomalacia; Burosumab.

## INTRODUCTION

X-linked hypophosphatemic rickets (XLHR) is the most common form of hereditary rickets, with a reported incidence of 1:20.000[1]. This life-long genetic disease is caused by loss-of-function mutations in the Phosphate Regulating gene with Homology to Endopeptidases (PHEX), expressed in osteocytes and odontoblasts[1]. These mutations result in increased circulating levels of fibroblast growth factor 23 (FGF-23), responsible for renal phosphate wasting through decreased tubular reabsorption and decreased 1-hydroxylation of 25-hydroxy-vitamin D (25-OH-D) to the active 1,25-dihydroxy-vitamin D (1,25-(OH)2-D), both resulting in chronic hypophosphatemia[2]. Additionally, increased FGF-23 levels have been associated with deleterious effects later in life, such as left ventricular hypertrophy and metabolic syndrome[2].

Clinically, the disease presents during the first or second year of life with growth retardation, delayed walking, and bone deformities, especially leg bowing[3], the latter frequently requiring corrective lengthening procedures[2]. When suspected, diagnosis is based on a low serum phosphate concentration, with reduced tubular reabsorption of phosphate corrected for glomerular filtration rate, based on standard values for age, and inappropriately low 1,25-(OH)2-D serum concentrations[3]. Genetic testing is mandatory[1].

Later in life, adults with XLHR are susceptible to osteomalacia[2]. Together with the abnormal mechanical stress linked to leg deformities, the latter predisposes to an increased risk of fractures and pseudofractures[2]. Osteoarthritis, enthesopathy, and muscle weakness further contribute to bone and joint pain, stiffness, decreased mobility, and disability, with impairment in the quality of life[3]. However, many adult patients are entirely asymptomatic.

Until recently, patients have had limited treatment options for this progressive and disabling condition. However, novel insights about the disease led to the development and approval of a treatment designed to target disease pathophysiology specifically.

## CASE REPORT

We report the case of a 50-year-old female diagnosed with sporadic XLHR, confirmed by genetic testing at the age of 25. The patient had been treated with adequate phosphate and calcitriol supplementation during childhood, although corrective surgery was required for bow deformities of the limbs. Once growth was complete, remission of symptoms led to treatment withdrawal, and only oral phosphate 500 mg twice daily was resumed for the last five years, in addition to calcium carbonate 1000 mg once a day.

The patient was referred to the rheumatology department in 2018 for incapacitating bone pain and a sense of diminished strength in her right limb with severe gait impairment, only possible with walking aids, developing for the past four weeks. There was no history of injury or trauma. Clinical examination revealed frontal bossing, depressed nasal bridge and limb bowing (Figure 1), hip and knee passive motion was free and painless, though crepitus was present. Muscle strength was preserved. The radiography of long bones revealed generalized osteopenia and a transverse radiolucent

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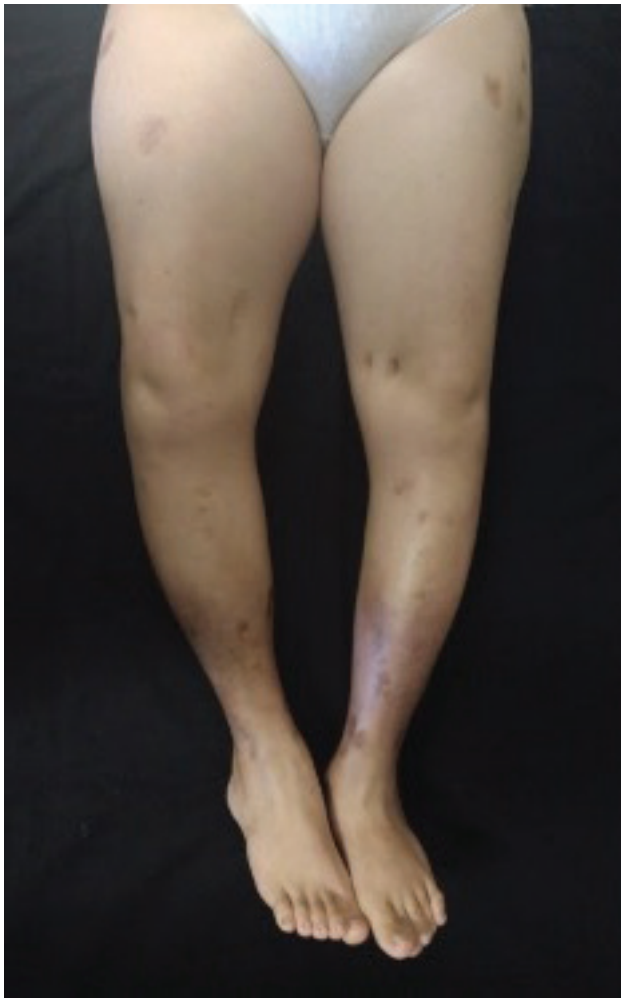


**Figure 1.** Bow deformity of inferior limbs

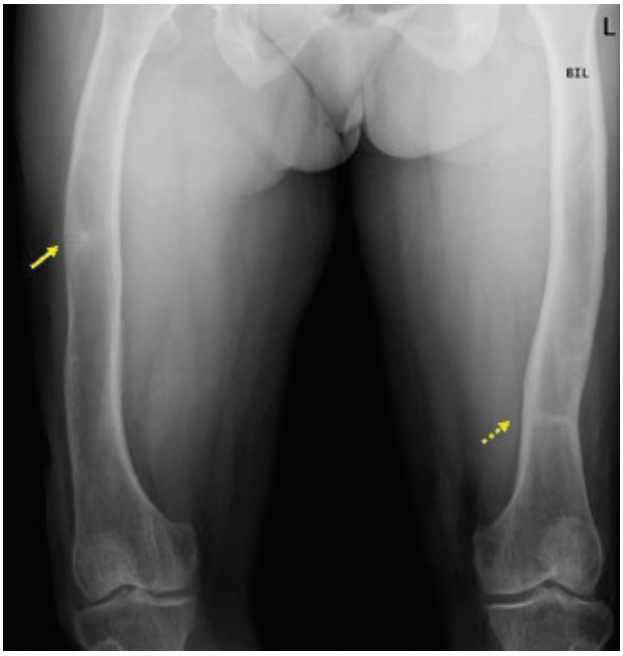



**Figure 2.** Radiography of long bones revealing a transverse radiolucent line with irregular sclerotic edges, consistent with a a pseudofracture ("Looser zone") in the right femoral diaphysis (arrow). Signs of previous lengthening procedures are detectable (dotted arrow).

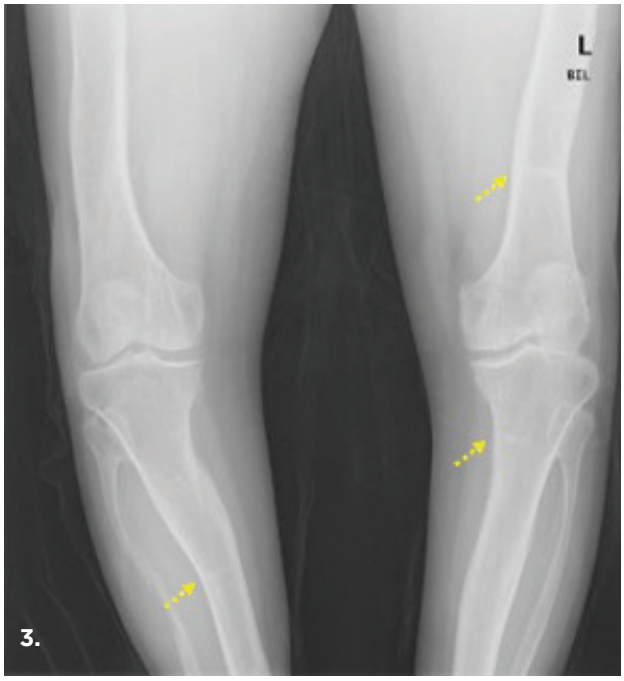
line in the diaphysis of the right femur with irregular sclerotic edges, consistent with a pseudofracture (Figure 2). Signs of previous lengthening procedures and arthrodesis of the left ankle were also observed (Figu-res 2-4). Laboratory analysis (Table I) revealed low serum calcium with elevated parathormone (PTH), hypophosphatemia, low 25-OH-vitamin D, and slightly elevated serum alkaline phosphatase. Measurement of 1,25-(OH)2-vitamin D was not accessible in our laboratory. Ultrasonography excluded nephrocalcinosis and nephrolithiasis. Dual-energy X-ray absorptiometry (DXA) revealed a T-score of –2.7 and of – 3.2 in the lumbar spine and total hip respectively.

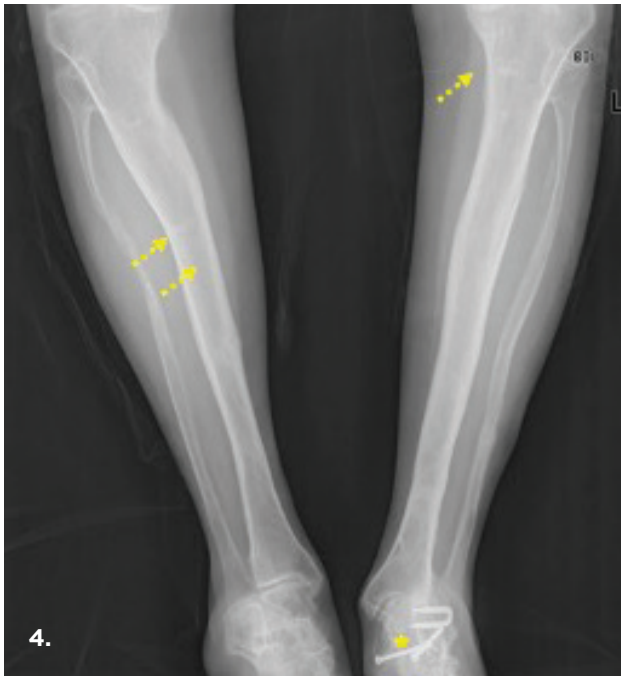
The pain was attributed to the pseudofracture, and superimposing secondary hyperparathyroidism was diagnosed. Therapy with calcitriol 0.25 ug daily was added, and conservative treatment was indicated for the fracture, with referral to rehabilitation medicine and proper analgesic therapy.

Six months later, the patient exhibited marked improvement of pain and was capable of walking without aids. After two years of follow-up, repeated DXA revealed a significant increase in bone mineral density (BMD) in the lumbar spine (+40.9%) and total hip (+32%), with T scores of 0.1 and -0.1, respectively. Regular monitoring with serum calcium, PTH, creatinine, and 24-hour calcium urinary excretion was performed.

## DISCUSSION

The adequate treatment of this disease is complex and therapeutic goals and indications vary throughout patients' lives. During childhood, early treatment with oral phosphate and calcitriol supplements aiming to normalize serum alkaline phosphatase levels is indicated. It has been shown to have beneficial effects on linear growth, bone deformities, and dental abnormalities[3]. In adult patients, it is generally accepted that treatment should be reinitiated (or maintained) in all symptomatic patients since it reduces bone pain and improves osteomalacia, muscle strength, and physical function[4]. However, overall treatment indications are controversial since its efficacy has not been precisely evaluated and due to concerns of aggravating hyperparathyroidism, with enhanced bone resorption, hypercalciuria, and nephrocalcinosis[2]. Actually, these patients frequently develop hyperparathyroidism. It is believed that deficient production of calcitriol[5] and recurrent stimulation of parathyroid glands by intermittent hyperphosphate-




**Figures 3 and 4.** Radiography of long bones revealing enlarged epiphyses and signs of previous lengthening procedures (dotted arrows). Figure 4 reveals signs of previous ankle arthrodesis (*).

**Table I. Laboratory findings on admission**

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|---|---|
| **Serum values** | |
| Calcium (mg/dL) | 8.5 (8-9-10.6) |
| Phosphate (mg/dL) | 1.7 (2.5-4.5) |
| PTH (pg/mL) | 150 (9-72) |
| 25-OH-D (ng/mL) | 23 (desirable > 29) |
| ALP (UI/L) | 125 (30-120) |
| Albumin (g/dL) | 3.7 (3.5-5.2) |
| Creatinine (mg/dL) | 0.58 (0.55-1.02) |
| **Urinary values** | |
| Urinary calcium 24h | 119 (<125) |

RALP: alkaline phosphatase; PTH: parathormone; 25-OH-D: 25-hydroxy-vitamin D

mia due to oral phosphate boluses[6] and are likely to play a significant role. Thus, when treatment in adults is indicated, calcitriol should be decreased to maintenance doses, and phosphate decreased to 700-1200 mg/day in two divided doses[2], aiming to relieve symptoms and not necessarily to normalize serum phosphate levels. Spontaneous insufficiency fractures and osteomalacia, specifically, should trigger treatment in adults, as it was reported to heal fractures earlier[7], decrease bone pain and reduce the extent of osteomalacia[4]. Additional recommendations include analgesics, non-steroidal-anti-inflammatory agents, physiotherapy, and physical exercise. However, this strategy fails to approach the long-term effects of increased FGF-23.

Burosumab is a recently developed recombinant human monoclonal antibody targeting FGF-23[8]. Previously approved for the treatment of children one year of age and older with XLHR, it was licensed in Europe in 2020 for use in adult patients, following the demonstration of safety and efficacy in increasing serum phosphate levels, accelerating fracture and pseudofracture healing, and improving osteomalacia in a phase 3 randomized, double-blind, placebo-controlled trial investigating the safety and efficacy of burosumab and in an open-label study investigating the effects of burosumab in osteomalacia in adult patients with XLHR[9-11], These studies also reported improved pain and stiffness, physical functioning and mobility. Furthermore, this novel therapy may provide a valuable tool in preventing hyperparathyroidism and the long-term metabolic effects due to FGF-23 excess observed in adult patients.

Because this report is about a single patient, the authors find it more suitable to express instructive remarks than conclusions. The authors underscore that adequate treatment with phosphate and calcitriol was effective in relieving symptoms and disability, highlighting the extent of increase in BMD observed. In fact, since adequate treatment was initiated our patient achieved and maintained good symptomatic and metabolic control of the disease. Secondly, although XLHR is a phosphate waste disorder, intuitive phosphate supplementation should never be given without calcitriol. Moreover, if secondary hyperparathyroidism develops, phosphate

doses should be decreased and calcitriol increased, with careful monitoring of calcium urinary excretion. Finally, adult patients suffering from this challenging disease are now eligible for a treatment that specifically targets the underlying mechanism, with proven efficacy and which may prevent some disease and treatment-related complications observed. Prescription of Burosumab is possible in Portuguese hospitals but currently limited to cases where adequate conventional treatment with phosphate and calcitriol fails in achieving symptomatic control of the disease, due to cost-effectivity reasons.

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