Received: 26 April 2022 | Revised: 10 June 2022 | Accepted: 23 July 2022

DOI: 10.1002/ccr3.6217

CASE REPORT

Clinical Case Reports Open Access WILEY

X-linked hypophosphatemic rickets: Case report of late diagnosis and bone pain improvement with targeted treatment

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Abstract

X-linked hypophosphatemia (XLH) is a rare disexase in which patients present with severe bowing of the legs, joint pain, and mobility problems. XLH has major adverse repercussions on the quality of life.

KEYWORDS

genetic, hypophosphatemia, pain, rickets

1 | CASE PRESENTATION

This article describes the case of a 43-year-old man, a primary school teacher, who reported musculoskeletal pain since childhood. He suffered predominantly from progressive joint pain, making it difficult to walk. The pain was associated with morning stiffness. The patient presented with significant growth retardation in addition to bone deformity, mainly in the legs, and genu valgum, which had required surgical treatment, namely, femoral and tibial osteotomy with intramedullary nailing when he was 14 years old. He reported no history of dental abscesses. The patient has 3 brothers who present alterations in their height, a 60-year-old sister, short stature and genu valgum, and 2 brothers aged 45 and 39 years with short stature, genu valgum, with mild functional limitation.

On physical examination, he showed normal vital signs, namely, a weight of 49 kg, height of 1.37 m, and body mass index of 26.2 kg/m^2. (Figure 1) Normocephalic, he showed adequate capillary implantation, but a flattened frontal bone; thick, horizontal eyebrows; downward palpebral fissures; a wide nasal bridge; a philtrum score of 2; low implanted ears; a short neck; teeth in poor condition; a symmetrical chest; rhizomelic shortening of the arms, but with no alterations of the hands; and genu valgum of the legs (Figure 2), but with no alterations of the feet. In

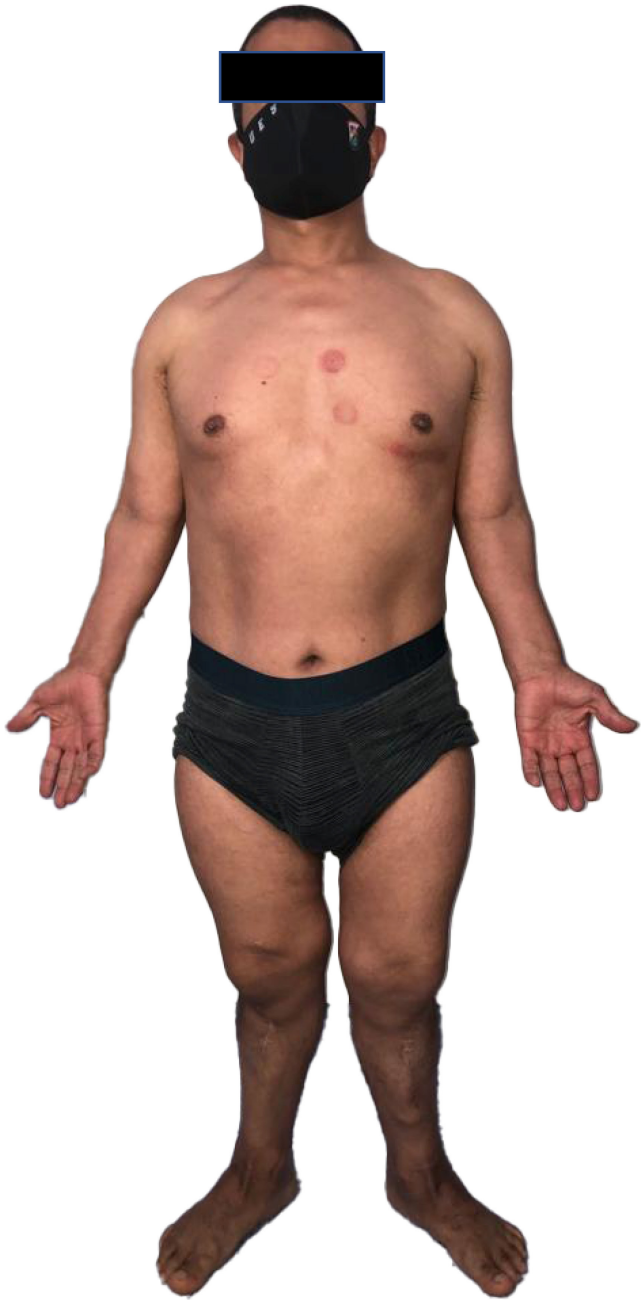

FIGURE 1 Short size. Physical examination

the dorso-lumbar region, he presented with scoliosis to the left. The upper-to-lower segment ratio (U/L) had a value of 0.74. On neurological examination, no alterations were detected.

The patient was not examined until his two-year-old daughter presented with delayed motor development, characterized by difficulty in walking and altered serum levels of phosphorus and parathyroid hormone.

For this reason, the same blood tests were performed on the patient, who showed hypophosphatemia and hyperparathyroidism, with normal calcium levels and increased alkaline phosphatase levels (Table 1). Radiographs of the long bones showed multiple deformities, with thickening and diaphyseal sclerotic areas of old fractures that exhibited changes due to chronic generalized osteoarthritis (Figures 3 and 4).

A clinical and molecular genetic study for skeletal dysplasias was performed, identifying a hemizygous variant in intron 15 of the PHEX gene, **c.1645+1G>A (p.Phe550fsX21)**, by massive parallel sequencing (Figure 5). The pathogenic variant found in the patient lay in an alternative splicing region described between exon 15 and intron 15, with a guanine substitution for adenine at position 1645 (c.1645+ 1G>A) in the latter. At the protein level, phenylalanine was replaced with a premature stop codon after 21 amino acids, thereby causing a frame shift. This change disrupts RNA splicing and results in an absent or altered protein product. The algorithms developed to predict the effect of such a sequence change in RNA splicing suggest that this variant can alter the consensus splice site and have a pathogenic effect. Based on these results, the patient was diagnosed and treated with phosphorus and calcitriol supplementation, which improved phosphate levels, reduced alkaline phosphatase levels, and led to a favorable clinical response by decreasing bone pain on follow-up examinations.

Initially, he was left with doses of 0.50 mcg of calcitriol twice daily and also mixtures of phosphates 300 mg three times a day, with this it was possible to maintain phosphorus levels within normal ranges and it was possible to reduce PTH values.

2 | DISCUSSION

Rickets is characterized by poor mineralization of the growth plate, which is usually associated with altered calcium and phosphorus levels and manifests as bone growth and development alterations. There are different forms of rickets. These include nutritional rickets, which results from a diet deficient in vitamin D, calcium, or phosphates; vitamin D-dependent rickets, which results from a deficiency in the metabolism of vitamin D; and hypophosphatemic rickets, which is resistant to vitamin D, secondary to a renal loss of phosphates.[1,2]

Hypophosphatemic rickets is a rare genetic disease, with an approximate incidence of 1 per 20,000 births in the European population.[3,4] The most common form of hereditary hypophosphatemic rickets is X-linked (XLH, which accounts for approximately 80% of familial cases of hypophosphatemia).[5] Despite the typical phenotype of the disease, data on disease incidence remains limited due to its infrequent presentation.[6] In Ecuador, no reported cases or statistics have been reported on its prevalence.

FIGURE 2 Genu valgum

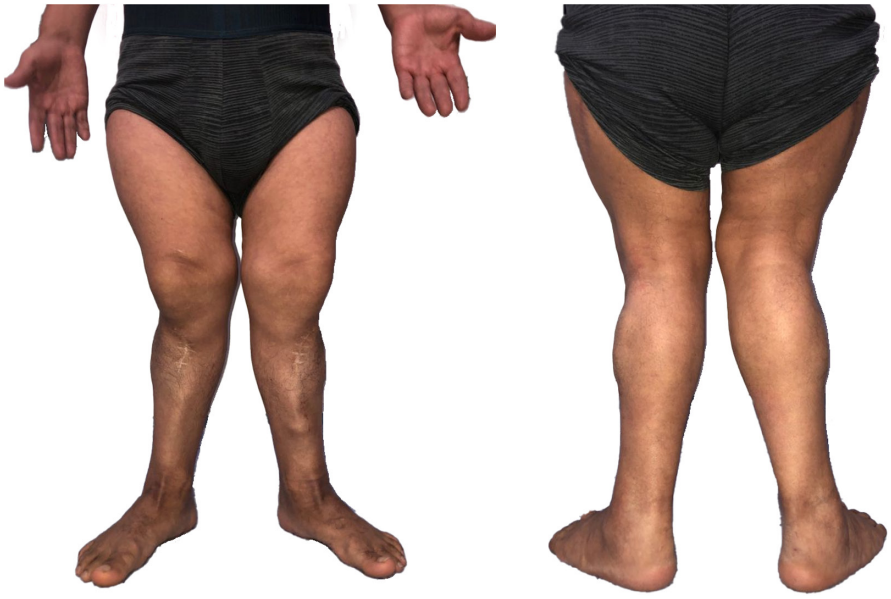

TABLE 1 Blood tests

	December 2020 (prior to treatment)	March, 2021	August, 2021	November, 2021	Reference ranges
Corrected calcium	9.54	8.56	9.59	10	8.1–10.2 mg/dl
Phosphorus	1.9	2.46	2.06		2.5–4.5 mg/dl
Albumin	4.7	5.01	4.95	4.6	3.5–5 gr/dl
Alkaline phosphatase	338	152	180		40–129 U/L
PTH	73.9		42.4		15–68.3 pg/ml
TSH	4.72				0.35–4.94 mIU/L
FT3	3.15				1.4–4.2 pg/ml
FT4	0.86				0.7–2 ng/ml
24-h urine calcium		64.1		55.04	100–321 mg/24 h
24-h urine phosphorus		0.6			0.4–1.3 g/24 h
24-h urine creatinine		47.87 (24-h urine volume: 2110 ml)			mg/dl
Calcitrol (1,25-dihydroxycholecalciferol)			51		30–70 pg/ml
Calcifediol (25-hydroxyvitamin D_3)	13.98		30		20–50 ng/ml
Tubular reabsorption of phosphate		99.26%			–

The clinical characteristics described in the literature are in line with those presented in this case. These include short height, growth retardation, ossification alterations, and bone pain symptoms; complementary studies have shown hypophosphatemia characteristic of the disease with increased levels of alkaline phosphatase and a low or inappropriately normal value of 1.25 OHD, in the context of hypophosphatemia.[7] XLH treatment is aimed at improving clinical manifestations, improving bone prognosis, and reducing complications to improve the quality of life.[8]

In addition to bone manifestations, dental alterations are commonly found in adult patients with XLH due to dental defects and poor quality of the dental enamel. These patients are prone to developing caries, root abscesses, periodontitis, tooth loss, and facial cellulitis.[9]

Currently, two types of therapy are recognized. Conventional treatment consists of administering oral phosphate salts combined with active derivatives of vitamin D (calcitriol), which improves musculoskeletal symptoms and increases bone mineralization.[10] The

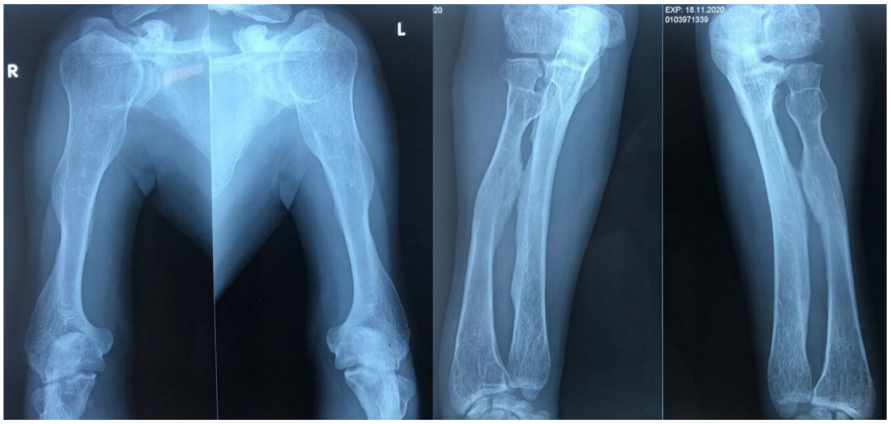

FIGURE 3 Radiograph of the long bones of the upper limbs show evidence of thinned cortical bone and joint irregularity with thickening and sclerotic areas, as well as diaphysis with varus deformities

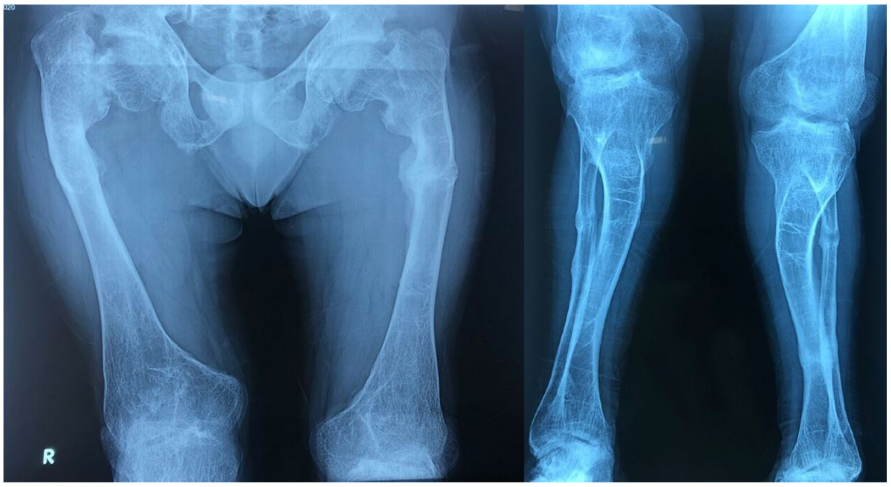

FIGURE 4 Radiographs of the long bones of the lower limbs show thinned bone cortices, with decreased bone density, varus deformity in thigh bones and valgus deformity in leg bones, hip joints with osteoarthritic changes, decreased joint space with marked subchondral sclerosis, and tibia and fibula diaphysis with valgus deformity with transverse sclerotic bands suggestive of old fractures

patient in this study received 0.50 mcg of calcitriol twice daily and also mixtures of phosphates 300 mg three times a day.

From the start of the therapy, biochemical follow-up was performed, which showed improvement in phosphorus levels, from 1.9 (prior to the treatment) to 2.46 and 2.06 mg/dl. Calcifediol levels increased after substitution therapy, from 13.98 to 30 ng/ml.

Although treatment with phosphorus salts and calcitriol increases phosphate bioavailability, it also increases FGF-23 levels, and can be associated with significant side effects, such as secondary hyperparathyroidism or nephrocalcinosis. For this reason, such a treatment should be closely monitored.[10]

The second type of therapy involves Burosumab, a monoclonal antibody that neutralizes FGF-23, a key factor in the pathophysiology of XLH. The recommended dose in adults is 1 mg/kg of weight, up to a maximum dose of 90 mg, administered every 4 weeks, with biochemical monitoring of phosphorus levels at least every 2 weeks. This medication reduced the renal excretion of phosphates. Clinical trials support its efficacy in reducing the clinical manifestations of the disease and improving bone prognosis and the quality of life, with minimal adverse effects. For this reason, Burosumab is considered a transformative agent in the treatment of this disease.[11]

3 | CONCLUSION

Although the diagnosis in the case of the reported patient was late, after the start of the treatment, there was an evident improvement in both biochemical and clinical manifestations; the importance of having established the diagnosis with certainty is highlighted, since more than improving the patient's quality of life, it is likely that starting specific treatment for your daughter will considerably improve her prognosis for bone development.

AUTHOR CONTRIBUTIONS

JB-C and PO-CH: case evaluation and patient management planning. AAR-B: case analysis. AR-S MA-A: patient genetic evaluation. AO-CH: manuscript revision and funding.

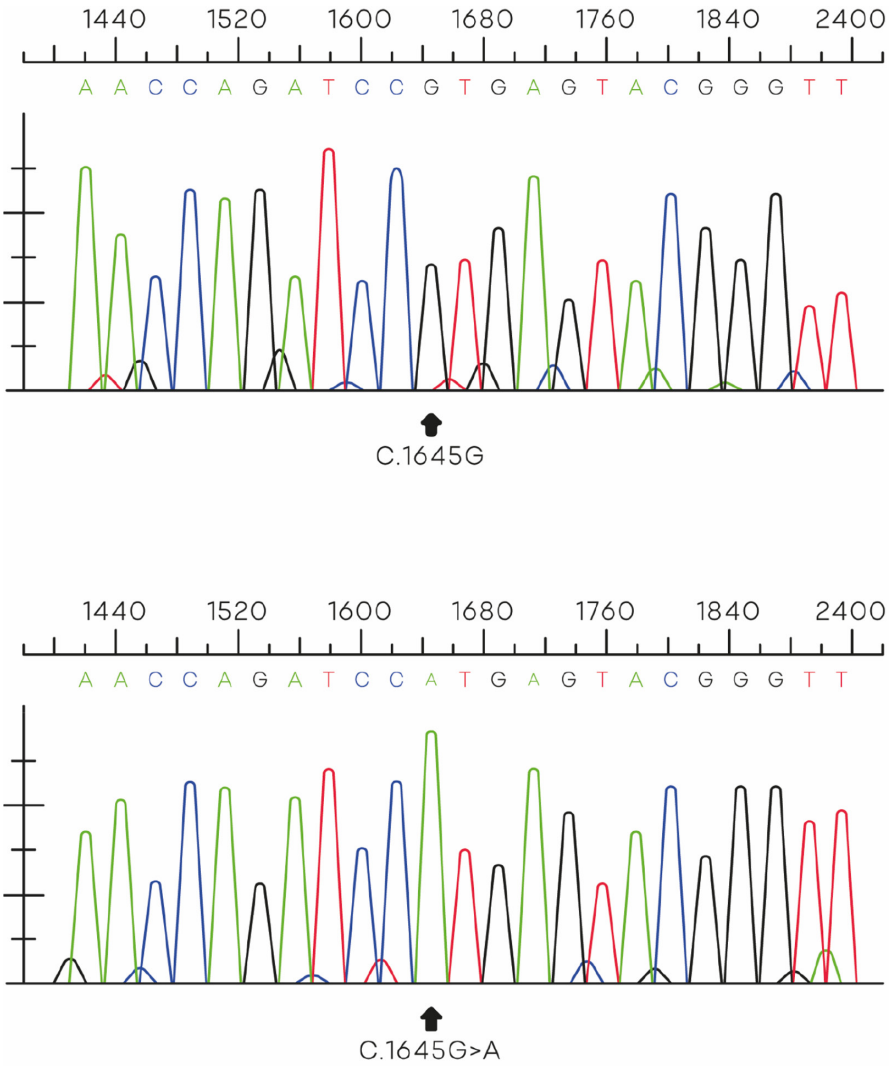

FIGURE 5 Genetic study, electropherogram

ACKNOWLEDGEMENTS

The authors thank the patient for his cooperation and consent in this case report.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

None.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Bermeo Cabrera MJ, Ordoñez Chacha PR, Reza-Albarrán AA, Ordoñez Chacha AK, Acero MA, Rodas Serrano A. X-linked hypophosphatemic rickets: Case report of late diagnosis and bone pain improvement with targeted treatment. *Clin Case Rep*. 2022;10:e06217. doi: 10.1002/ccr3.6217