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Therapeutic Response to Burosumab in a Child with X-Linked Hypophosphatemia: A Case Report

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Abstract: ***X-linked hypophosphatemic rickets (XLH) is a rare disorder caused by mutations in the PHEX gene, resulting in the overexpression of fibroblast growth factor 23 (FGF23), a hormone that decreases renal phosphate reabsorption and active vitamin D synthesis. This report presents the case of a 3-year-old girl clinically diagnosed with XLH, presenting with bone deformities such as genu valgum, delayed motor development, and dysmorphic features. The diagnosis was confirmed through genetic testing identifying a pathogenic variant in the PHEX gene. The patient was treated with burosumab, a monoclonal antibody that inhibits FGF23. Following treatment, significant improvements were observed, including an increase in serum phosphate levels and decreases in alkaline phosphatase and parathyroid hormone (PTH) levels, demonstrating burosumab's role in improving clinical outcomes.***

Keywords: X-linked hypophosphatemic rickets, XLH, Burosumab, FGF23, pediatric, case report

1. Introduction

Hypophosphatemic rickets comprises a group of disorders characterized by systemic hypophosphatemia, usually due to excessive renal phosphate wasting (1). This condition can be classified into hereditary and acquired forms and is further subdivided based on the underlying pathophysiological mechanism into fibroblast growth factor 23 (FGF23)-dependent and FGF23-independent types (1, 2). FGF23 is a phosphaturic hormone produced by osteocytes that primarily functions to inhibit renal phosphate reabsorption (2).

The most prevalent hereditary form is X-linked hypophosphatemic rickets (XLH), caused by inactivating mutations in the *PHEX* (phosphate-regulating endopeptidase homolog, X-linked) gene (3). These mutations result in FGF23 overexpression, leading to decreased proximal tubular phosphate reabsorption and reduced synthesis of 1,25-dihydroxyvitamin D (calcitriol) (3). Although the true prevalence may be underreported due to diagnostic challenges, studies report frequencies ranging from 1.33 to 1.6 cases per 100,000 children (4). Clinical manifestations typically include lower limb deformities (e.g., genu varum, genu valgum), bone pain, arthralgias, impaired growth leading to short stature, and dental abnormalities (5).

The diagnosis of XLH relies on clinical features combined with characteristic biochemical findings: persistent hypophosphatemia with reduced tubular reabsorption of phosphate, elevated alkaline phosphatase (ALP) activity, and normal or inappropriately low serum levels of 1,25-dihydroxyvitamin D relative to the hypophosphatemia (6). Definitive diagnosis is established through genetic testing identifying pathogenic variants in the *PHEX* gene (7). Conventional treatment involves oral phosphate supplementation combined with active vitamin D metabolites (e.g., calcitriol) (8). More recently, burosumab, a monoclonal antibody targeting FGF23, has demonstrated efficacy in normalizing serum phosphate levels, improving tubular phosphate reabsorption, promoting the healing of rickets, and enhancing physical function (9,10).

This case report aims to document the clinical presentation, diagnostic process, and treatment response of a pediatric XLH patient receiving burosumab.

2. Clinical Case

A 3-year and 4-month-old female preschooler was referred to pediatric endocrinology for evaluation of short stature, severe genu valgum, and flat feet, findings suggestive of a metabolic bone disorder. She was the product of a second pregnancy with adequate prenatal care, delivered preterm at 34.5 weeks via cesarean section due to oligohydramnios. Birth weight and length were appropriate for gestational age, and Neonatal Intensive Care Unit (NICU) admission was not required. She achieved sitting at 18 months and began walking independently at 20 months, which indicated a delay in motor development. Family history was notable for a fourth-degree relative with genu valgum; no other relevant conditions were reported. The patient had been initially assessed by Orthopedics for suspected rickets, leading to empiric treatment with oral calcium and vitamin D supplements.

On physical examination, her weight-for-height and body mass index (BMI) were both above +2 standard deviations (SD), height-for-age was below -2 SD, and head circumference was at the mean for age (0 SD). Dysmorphic features included a broad and prominent forehead, flat nasal bridge, long philtrum, short neck, bell-shaped thorax, costal rosary, and Harrison's groove. Musculoskeletal findings comprised wrist hyperlaxity, Madelung-like deformity, flexible flat feet, and severe genu valgum.

Initial laboratory testing showed: PTH 77.3 pg/mL (normal range typically <65 pg/mL), serum calcium 9.39 mg/dL, 25-hydroxyvitamin D 28.4 ng/mL (indicating insufficiency), ALP 801 U/L (significantly elevated), and serum phosphate 3.51

mg/dL (low for age). Radiographs of the lower limbs revealed severe genu valgum with distal femoral metaphyseal flaring in a "champagne glass" configuration.

Based on the clinical presentation, biochemical profile (hypophosphatemia, high ALP, inappropriately normal PTH for the phosphate level), and radiologic findings, XLH was suspected. Genetic testing was initiated. At age 4, the patient underwent surgical correction (hemiepiphysiodesis) of the genu valgum (Figure 1).

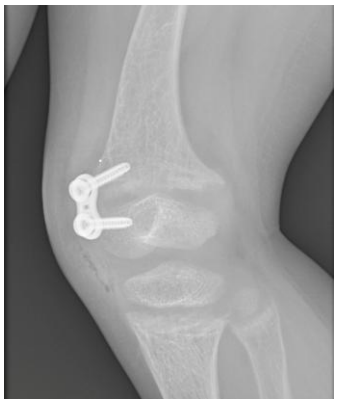
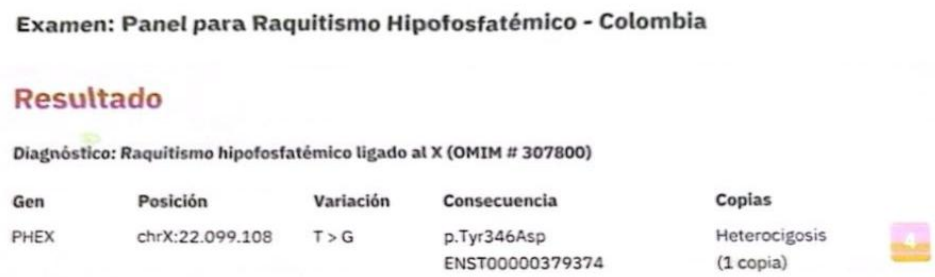


Figure 1: Radiograph of the right knee status post-hemiepiphysiodesis. Surgical hardware is visible at the distal femur. Note is made of metaphyseal changes consistent with rickets and generalized osteopenia

One month post-surgery, genetic testing confirmed a heterozygous pathogenic variant in the *PHEX* gene (chrX:22,099,108 T>G; p.Tyr346Asp) (Figure 2), confirming the diagnosis of XLH.



Examen: Panel para Raquitismo Hipofosfatémico - Colombia

Resultado

Diagnóstico: Raquitismo hipofosfatémico ligado al X (OMIM # 307800)

Gen	Posición	Variación	Consecuencia	Copias
PHEX	chrX:22.099.108	T > G	p.Tyr346Asp ENST00000379374	Heterocigosis (1 copia)

Figure 2: Genetic testing result confirming a heterozygous likely pathogenic variant (p.Tyr346Asp) in the *PHEX* gene, consistent with X-linked hypophosphatemic rickets.

Burosumab therapy was initiated at 10 mg subcutaneously every two weeks. After six months of treatment, follow-up laboratory tests showed improvement: ALP decreased to 770 U/L, serum phosphate increased to 4.5 mg/dL (normal range), serum calcium was 11.6 mg/dL (monitored, potentially related to therapy initiation or assay variability, considered acceptable), and PTH normalized to 12.6 pg/mL. Renal and urinary tract ultrasounds remained normal. Continuation of burosumab therapy and ongoing multidisciplinary follow-up were recommended.

3. Discussion

XLH is the most common form of hereditary hypophosphatemic rickets, typically presenting within the first two years of life as skeletal deformities become apparent with weight-bearing and walking (11). This case report details the presentation of a young girl whose clinical course aligns with the natural history described in the literature. Key features included delayed attainment of gross motor milestones (sitting, walking), significant short stature (height-for-age < -2 SD), and characteristic skeletal deformities like severe genu valgum and flat feet. These manifestations are primarily due to chronic hypophosphatemia that disrupts bone mineralization by impairing chondrocyte and osteoblast function. The resulting structural abnormalities in the lower limbs compromise alignment and stability for ambulation and disrupt normal growth plate function, further impairing linear growth (12). Other classic phenotypic features observed, such as the rachitic rosary and Harrison's groove, result from abnormal cartilage growth at the costochondral junctions and altered rib morphology due to respiratory muscle pull on softened bone, respectively (13).

Biochemically, XLH is characterized by excessive FGF23 production due to *PHEX* inactivation. Elevated FGF23 levels cause renal phosphate wasting by downregulating sodium-phosphate cotransporters in the proximal tubules. Furthermore, FGF23 inhibits the enzyme 1-alpha-hydroxylase, responsible for converting 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D (calcitriol), and enhances the activity of 24-hydroxylase, which catabolizes calcitriol, thus contributing

to inappropriately normal or low calcitriol levels despite hypophosphatemia (14, 15). While significant hypocalcemia is uncommon, transient dips can stimulate a secondary hyperparathyroidism, although PTH levels are often within the normal or only slightly elevated range (13) . Markedly elevated ALP activity is a hallmark, reflecting increased osteoblastic activity secondary to impaired mineralization (13, 16). While useful for monitoring treatment response, ALP levels alone have limitations for diagnosis, necessitating correlation with clinical findings, imaging, and potentially standardized tools like the Rickets Severity Score (RSS) (16).

The therapeutic strategy for XLH aims to correct phosphate deficiency and mitigate the effects of excess FGF23. Conventional therapy with oral phosphate salts and active vitamin D analogs can improve biochemical parameters and rickets but often requires frequent dosing, carries risks (e.g., nephrocalcinosis, hyperparathyroidism), and may not fully normalize growth or heal skeletal lesions (8, 13). Burosumab, by directly inhibiting FGF23, addresses the underlying pathophysiology more effectively. Clinical trials have demonstrated its superiority over conventional therapy in normalizing serum phosphate, improving renal phosphate reabsorption, healing rickets, reducing pain, improving growth, and enhancing physical function in pediatric patients (9, 10, 17, 18). In this case, treatment with burosumab led to a favorable biochemical response, evidenced by increased serum phosphate, decreased ALP activity, and normalized PTH levels within six months, indicating improved mineral homeostasis and bone metabolism.

4. Conclusion

This case illustrates a typical presentation of XLH in a young child, characterized by short stature, delayed motor development, and significant skeletal deformities secondary to chronic hypophosphatemia caused by a pathogenic *PHEX* mutation. Diagnosis was confirmed via clinical, biochemical, radiographic, and genetic findings. Treatment with the FGF23-inhibiting monoclonal antibody, burosumab, resulted in significant improvement in key biochemical markers of mineral metabolism within the initial six months. This case underscores the effectiveness of targeted therapy with burosumab in managing the pathophysiological consequences of XLH in pediatric patients and highlights the importance of multidisciplinary care involving endocrinology, orthopedics, and genetics for optimal patient outcomes. This case adds to the growing body of evidence supporting early targeted therapy to improve long-term outcomes in pediatric XLH. Further follow-up will assess the long-term impact on growth, skeletal health, and functional abilities. Continued monitoring will be essential to assess the durability of these improvements and overall quality of life.

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