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NEPHROLOGICAL EVOLUTION OF PEDIATRIC PATIENTS WITH X-LINKED HYPOPHOSPHATEMIC RICKETS. CASE SERIES

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ABSTRACT

X-linked hypophosphatemic rickets (XLR) is a rare inherited disease characterized by abnormalities in phosphorus metabolism caused by a mutation in the PHEX gene. Biochemically, it is characterized by hypophosphatemia secondary to hyperphosphaturia and vitamin D deficiency, and clinically by bone deformities in the lower extremities and growth retardation. Conventional treatment with phosphate salts and active vitamin D has been used for over 45 years; however, it has been associated with nephrocalcinosis. Currently, a new medication for the treatment of XLR, a monoclonal antibody called Burosumab, is available and was approved for use in 2018. ***Method****:* A search was conducted of the medical records of pediatric patients diagnosed with X-linked hypophosphatemic rickets treated with burosumab, and biochemical parameters were analyzed throughout their clinical course. ***Results****:* Before burosumab administration, the patients presented with hypophosphatemia, decreased tubular reabsorption of phosphorus, insufficient vitamin D, and hypercalciuria in one patient. After 12 months of burosumab treatment, these parameters improved. ***Conclusion****:* This study provides evidence of the initial response to Burosumab treatment in pediatric patients, where biochemical improvement was observed with the introduction of Burosumab into the treatment regimen for patients with XLR, thus reducing the risk of nephrocalcinosis.

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INTRODUCTION

X-linked hypophosphatemic rickets (XLR), or familial hypophosphatemic rickets, is a rare disease. In most cases, it is a genetic disorder with complete penetrance and an X-linked dominant pattern. It is caused by a mutation in the PHEX gene, located at Xp22.1. This gene encodes the cell surface protein cleavage enzyme PHEX (Phosphate-Regulating Neutral Endopeptidase), which is expressed in osteoblasts, osteocytes, and teeth. When PHEX function is impaired, there is increased production of Fibroblast Growth Factor 23 (FGF23), which is primarily produced by osteocytes. [i] [ii] X-linked hypophosphatemic rickets comprises 85–90% of all hypophosphatemic rickets cases, with an incidence of 3.9 per 100,000 live births and a prevalence of 1.7 to 4.8 per 100,000 individuals. The male-to-female ratio is 1:2 and increases progressively during adulthood. This molecular mutation was first reported in 1995. [2] [iii]

In the kidneys, specifically in the proximal convoluted tubule, phosphate transport is mediated by sodium-phosphate cotransporters (NaPi). There are three types of NaPi, with type IIa being the most important, responsible for 70% of total phosphate reabsorption. Increased FGF23 levels reduce the expression of NaPi type IIa and IIc cotransporters, resulting in decreased phosphate absorption and excretion. Furthermore, the reduced expression of 1-hydroxylase and 24-hydroxylase enzymes leads to decreased production of the active metabolite of vitamin D (1,25-dihydroxyvitamin D), further reducing phosphate absorption in the intestine. [3] [iv] Clinical manifestations can be evident as early as 6 months of age with lower limb deformities, primarily bowing of the femur and tibia (genu varum), widening of the distal metaphyses in the wrists and ankles, and thickening of the costochondral junctions. By age 2, an abnormal gait or waddling gait is present. Dental abscesses may appear by age 3. Biochemically, there will be hypophosphatemia secondary to hyperphosphaturia, decreased $1,25(OH)_2$, normal or elevated PTH, and in some cases, elevated alkaline phosphatase and hypercalciuria. The diagnosis is

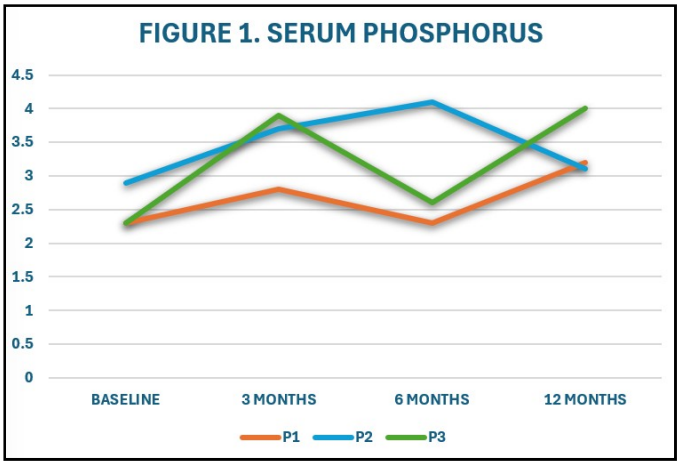
confirmed in 70–99% of cases with genetic testing that reveals a pathological alteration of the PHEX gene. [2] [4] [v] Since 1975, conventional treatment based on phosphate salts and active vitamin D has been used to prevent new lesions and deformities, maintain normal PTH concentrations, and optimize growth. However, conventional therapy does not improve tubular reabsorption of phosphorus and has been associated with hypercalciuria and nephrocalcinosis. In 2018, the FDA approved the use of Burosumab, a fully human IgG1 monoclonal antibody, for the treatment of X-linked hypophosphatemic rickets. Its action lies in the binding and inhibition of FGF23. Its half-life is 13 to 19 days, so it must be administered every 2 weeks. [vi] In 2023, TAO Jia-Qi et al. conducted a retrospective study at the Children's Hospital of Nanjing Medical University, including a total of 83 children with X-linked hypophosphatemic rickets. At the time of initial diagnosis, 55% of the children had short stature (≤ -2 SD) and 35% had a height between -2 SD and -1 SD. Factors that both influence and do not influence the development of nephrocalcinosis in these patients were identified. Serum calcium and TMP/GFR were lower in the group with nephrocalcinosis, while PTH and urinary calcium were higher in this same group. The study concluded that, after analytical analysis of the results, TMP/GFR and urinary calcium are closely related to nephrocalcinosis.[vii] Anthony A. Portale et al., in 2024, analyzed 196 children and 318 adults with XLH. Ninety-seven percent of the children and 94% of the adults had previously received conventional therapy with oral phosphate salts and vitamin D. Nephrocalcinosis was detected in 22% of the children and 38% of the adults. A glomerular filtration rate (GFR) <90 mL/min/0.73 m² was associated with nephrocalcinosis in the group of children, who also presented with low TMP/GFR ratios, decreased $1,25(OH)_2D$, and elevated serum calcium. The authors concluded that nephrocalcinosis was observed in almost a quarter of the children and more than a third of the adults with XLH and stated that further studies are needed to better understand the factors that cause nephrocalcinosis in these patients. [viii]

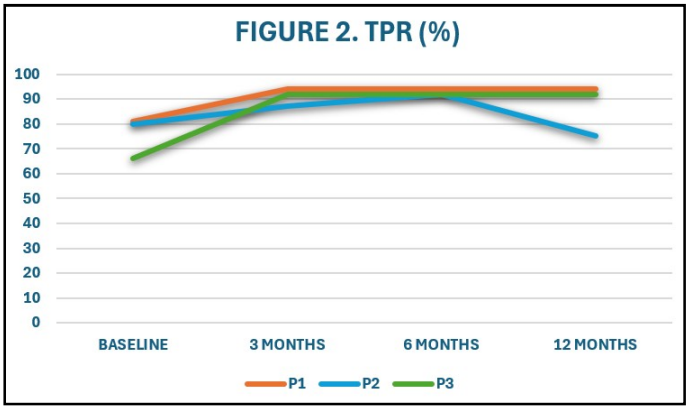
ANALYSIS METHODOLOGY

The Integrated Medical-Administrative Information System (SIIMA) of the Hospital de la Niñez Poblana was searched for patient records of children aged 0 to 17 years 11 months diagnosed with X-linked hypophosphatemic rickets who were currently receiving treatment with the monoclonal antibody burosumab. Serum phosphorus, 24-hour urinary phosphorus, tubular reabsorption of phosphorus (TRP), parathyroid hormone, serum calcium, 24-hour urinary calcium, vitamin D, and serum creatinine levels were analyzed, and ultrasound scans were performed before and after treatment. Baseline values were those of the patients before starting burosumab, and changes were analyzed at 3, 6, and 12 months post-treatment. Three patient records were found with a confirmed diagnosis of X-linked hypophosphatemic rickets. Patient P1 had been on conventional treatment for 11 years and her first Burosumab application was at age 11; patient P2 had her first application at age 9 and had been on conventional treatment for 6 years; and patient P3 did not have conventional treatment, but started with Burosumab from age 4. This research study will be conducted under the guidelines of documents that govern research involving human subjects, such as the 1979 Belmont Report, which outlines the ethical principles that must be followed: autonomy, beneficence, non-maleficence, and justice; and the 1991 Rule of the Commons, which protects vulnerable subjects such as pregnant women, prisoners, and children, the latter being our case. Finally, we will be guided by the principles of the 1964 Declaration of Helsinki, which addresses the well-being, health, and rights of the patient, and stipulates that the research protocol must be reviewed by an independent committee before commencement and that research must be conducted by qualified personnel. The Nuremberg Code, published in 1948, states that "the voluntary consent of the subject is absolutely essential." According to Article 17 of the Regulations of the General Health Law on Health Research, which came into effect in 1984, this research is categorized as "low-risk research" since it employs retrospective documentary research techniques.

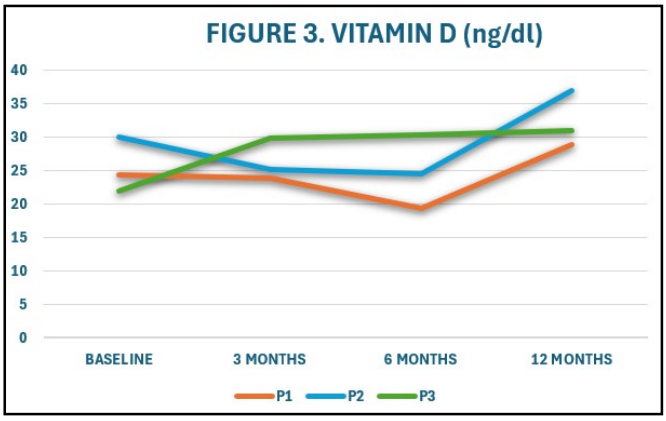
RESULTS

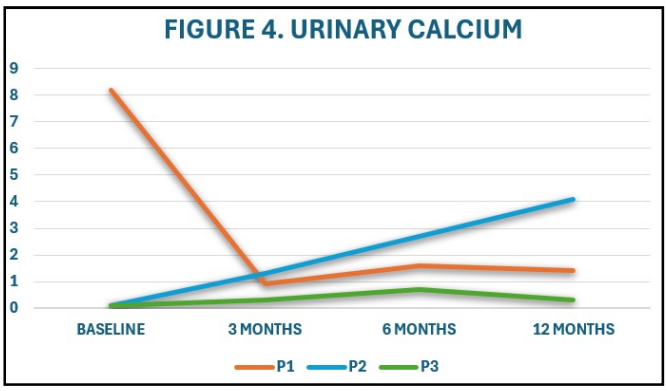
In this study, baseline values (before treatment with Burosumab) were below the normal range for age. Patients P1 and P2 were 9 years old, with baseline serum phosphorus levels of 2.3 mg/dL and 2.9 mg/dL, respectively (low). Patient P3 was 3 years old, and her baseline serum phosphorus level was also 2.3 mg/dL (low). After Burosumab administration, levels increased, and after 12 months of treatment, patient P1, aged 15 years, had a serum phosphorus level of 3.3 mg/dL (normal for her age), patient P2, aged 10 years, had a serum phosphorus level of 3.1 mg/dL (low for her age, but with an upward trend), and patient P3 had a serum phosphorus level of 4 mg/dL (normal for her age) (Figure 1). Two of the patients developed hyperphosphaturia while receiving conventional treatment. Baseline Total Phosphorus Reabsorption (TPR) levels for patients P1, P2, and P3 were 81%, 80%, and 66%, respectively, placing them at the lower limit of normal. Six months after treatment with Burosumab, a considerable increase was observed in all three patients, with values of 94%, 92%, and 92%, respectively. After 12 months of treatment, these values remained stable, except in patient P2. This was most likely due to the fact that she did not receive Burosumab in month 11 because of a lack of resources at the institution (Figure 2).





The baseline vitamin D levels of patients P1, P2, and P3 were insufficient, with values of 24.3 ng/dl, 29.9 ng/dl, and 21.9 ng/dl respectively. After 12 months of treatment, the values in patients P2 and P3 rose to 36.9 ng/dl and 30.9 ng/dl respectively; however, in patient P1, the vitamin D level was deficient with a value of 19.2 ng/dl (Figure 3). The normal range for 24-hour urinary calcium is 1 to 4 mg/kg/day. Patient P1 began treatment with conventional therapy and continued it for 11 consecutive years. She began treatment with Burosumab at age 14. Her baseline urinary calcium was 8 mg/kg/day. In the following months, her urinary calcium decreased considerably and remained below 2 mg/kg/day.





Patients P2 and P3 began treatment with Burosumab at ages 9 and 3, respectively. Patient P2 received only 3 years of conventional treatment and subsequently continued treatment with the monoclonal antibody. Her baseline urinary calcium was 0.1 mg/kg/day. Finally, patient P3 did not receive conventional treatment; her initial treatment was with Burosumab, and her baseline calcium was also 0.1 mg/kg/day. (Figure 4) PTH, calcium, and creatinine levels remained within normal ranges before and after treatment. Imaging studies were intentionally sought to rule out nephrocalcinosis; both ultrasounds performed before treatment with Burosumab and more recent ultrasounds have reported normal sonographic characteristics, with no dilations and no evidence of kidney stones.

DISCUSSION

In this case series, biochemical parameters were analyzed in 3 patients diagnosed with X-linked Hypophosphatemic Rickets confirmed by genetic study that evidenced the pathogenic variant of the PHEX gene. It is important to mention that, during the time of administration of the medication, there were periods of time in which the hospital did not have the resource, so it could not be administered to the patients. Before starting treatment with Burosumab, all three patients had marked hypophosphatemia, low or borderline PTH, and vitamin D deficiency. These are the most characteristic parameters in patients with this condition. However, after treatment with the mononuclear antibody, the levels changed with a trend toward improvement. Nevertheless, due to a lack of medication in the hospital at different times during treatment, we encountered unexpected altered values. For example, patient P2 had decreased PTH (<75%) in month 12 of treatment; patient P3 had considerably elevated PTH (104.9 pg/dl) despite 3 months of Burosumab treatment; and all three patients had insufficient vitamin D levels. It was only after 12 months that sufficient levels (>30 ng/dl) were reached in two patients (P2 and P3), while patient P1 had a deficient level of 19.2 ng/dl. Serum creatinine and calcium levels remained within normal limits, with no evidence of acute kidney injury. Urinary calcium is a risk indicator for the development of kidney stones.

Conventional treatment for HLH is based on phosphate salts and calcitriol. According to de Lucas Collantes et al., conventional treatment, specifically the administration of active vitamin D or calcitriol, is associated with hypercalciuria and nephrocalcinosis. Switching from conventional treatment to the monoclonal antibody burosumab reduces this risk. In the case of patient P1, baseline urinary calcium was elevated while on conventional treatment; however, since starting burosumab administration, levels have decreased considerably, reducing the risk of nephrocalcinosis. On the other hand, patients P2 and P3 did not experience hypercalciuria at any point, likely because burosumab was administered at a young age. Finally, renal ultrasound analysis of all patients showed no evidence of kidney stones at any time to date.

CONCLUSIONS

X-linked hypophosphatemic rickets is a rare disease that has undergone a significant therapeutic shift that could benefit patients. With the introduction of the monoclonal antibody burosumab, both clinical and biochemical improvements have been observed, reducing the risk of nephrocalcinosis, a complication previously associated with conventional treatment. This study provides evidence of the initial response to burosumab treatment; however, continued patient monitoring is necessary to determine the long-term renal consequences.

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