Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 06/16/2020
Approved on: 03/09/2021

CASE REPORT

X-linked hypophosphatemic rickets: case report

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Keywords:
Rickets,
Hypophosphatemic,
Genetic Diseases,
X-Linked,
Bone Diseases,
Metabolic.

Abstract

Introduction: The X-linked hypophosphatemic rickets is considered the most common cause of rickets. It is an X-linked dominant disease, caused by a PHEX gene mutation. It is believed that the biochemical and bone mineralization changes because of the increase of phosphaturic factor, resulting from the PHEX genes inability to inactivate its substrate. **Case Report:** A seven-year and eleven-month-old girl has been followed by an orthopedist since she was 1 year old, due to lower limb deformity. She was referred to a pediatric endocrinologist for further evaluation. At clinical examination, the patient presented *genu varum* and Z score of stature/age = 4.8. Laboratory tests: serum phosphorus = 2.3mg/dl (4.5-6.6), ionic calcium = 1,8mmol/l (1.17-1.32), parathyroid hormone = 42pg/ml (12-88), alkaline phosphatase = 600U/L (<300). The patient has always shown low adherence to treatment. Currently, at age 12 and 2 months old, endures with *genu varum* and short stature, besides the persistence of laboratory alterations. The PHEX gene sequencing, that evidenced a heterozygous mutation on that gene, confirming the X-linked hypophosphatemic rickets diagnosis. **Comments:** The X-linked hypophosphatemic rickets is a rare disease with clinical manifestations observed since the early years of life. Diagnosis and intervention are important to decrease these patients morbimortality. The patient started follow-up at our service belatedly, with bone deformity and short stature, resulting in low treatment adherence. For these reasons, there wasnt any clinical or laboratory improvement during that time.

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DOI: 10.25060/residpediatr-2022.v12n3-336

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INTRODUCTION

Rickets is characterized by failure or delay in mineralization of the newly formed osteoid matrix during the process of endochondral ossification in the growth plate. The causes of rickets involve deficiency of calcium, vitamin D and phosphorus, as well as changes in the metabolism or vitamin D action[1,2].

There are some syndromes that present isolated renal phosphate loss, resulting in hypophosphatemia, normocalcemia and primary rickets[3,4]. This clinical picture is caused by increased levels of bone-derived fibroblast growth factor 23 (FGF-23) which prevents adequate reabsorption of phosphate in the renal tubule and interferes with renal hydroxylation of vitamin D[5,6].

The genes involved and the model of inheritance of this syndrome may be diverse, with X-linked hypophosphatemic rickets being considered the most common cause of hereditary rickets, with a prevalence ranging from 1.7 per 100,000 children to 4.8 per 100,000 individuals including adults and children[7]. This form of presentation is caused by mutations in the PHEX gene, located in Xp22.1, which encodes the expression and degradation of FGF-23[1,8].

The definitive diagnosis of the disease is made through molecular investigation, but physical examination and routine laboratory and radiological evaluation can guide the diagnostic investigation, enabling early treatment of the disease[3].

The treatment has as main objectives the reduction of skeletal deformities and growth rate improvement, being carried out with the replacement of phosphorus and calcitriol. Early treatment can reduce the intensity of growth retardation and lower limb deformities[3,9].

Burosumab, also indicated in this condition, is a monoclonal antibody with action to recognize and bind to the FGF23 protein, blocking its activity, which allows the kidneys to reabsorb phosphate and restore normal levels of phosphate in the blood. It also allows the hydroxylation of vitamin D by the kidneys, increasing the levels of calcitriol, the active form of vitamin D[10,11].

This paper aims to report a case of a patient with X-linked hypophosphatemic rickets, describing her clinical and laboratory characteristics of the disease, alerting to the early diagnosis of this rare condition.

CASE REPORT

Girl, 7 years and 11 months old, followed by orthopedics since 1 year of age, due to deformity in the lower limbs. Referred to pediatric endocrinology for evaluation.



Figure 1. lower limbs *Genuvarum*.

At the first consultation at 7 years and 11 months of age, she had genu varum (figure 1) and short stature (SDS height/age = -4.8). Laboratory tests: serum phosphorus = 2.3 mg/dL (4.5 - 6.6), ionic calcium = 1.8 mmol/L (1.17 - 1.32), parathyroid hormone = 42 pg/mL (12 - 88), alkaline phosphatase = 600 U/L (< 300). Phosphorus and calcitriol replacement was started, but she always showed poor treatment compliance. Table 1 describes the patient's clinical and laboratory evolution during follow-up with pediatric endocrinology.

Currently, at 12 years and 2 months, she remains with genu varum and short stature (SDS height/age = -4.48) and complains of bone pain. Laboratory tests: alkaline phosphatase = 415 U/L (< 300), ionic calcium = 1.25 mmol/L (1.17 - 1.32), serum phosphorus = 2.5 mg/dL (4 - 7), parathyroid hormone = 37 pg/ml (12 - 88), vitamin D = 18.5 ng/ml (20 -280). The PHEX gene sequencing was performed, which showed a heterozygous mutation in this gene, confirming the diagnosis of X-linked hypophosphatemic rickets.

Comments

Patients with X-linked hypophosphatemic rickets have normal height at birth and reduced growth velocity during the first few years of life. After the onset of ambulation, the typical clinical manifestations of the disease develop, characterized by short stature and deformities in the lower limbs (genu varum or genu valgum)[1].

Table 1. Clinical and laboratorial Evolution of the patient under investigation during follow-up at the pediatric endocrinology department.

Age	7y 11m	8y 2m	8y 8m	10y 2m	11y 8m	12y 2m
Stature (cm)	99	103.2	104	112	119	121
Z Score statue/age	- 4.8	- 4.46	- 4.65	- 4.32	- 4.4	- 4.48
BMI (kg/m²)	20.18	19.5	20.2	28	24.9	26.16
Z score BMI	+ 1.54	+ 1.31	+ 1.41	+ 1.59	+ 1.82	+ 2.20
Ca (mg/dL)		9.7				10.10
Ion Ca (mg/dL)	1.08	1.21				1.25
P (mg/dL)	2.3	2.4				2.5
PTH (ng/L)	42	19.4				17
FA (U/L)		600				415
Vitamin D (ng/mL)	25.2					18.5

y: years; m: months; E: stature; BMI: body-mass index; Ca: calcium (RV: 8.5 - 10.2); ion Ca: ion calcium (RV: 1.17 - 1.32); P: phosphorus (RV: 4 - 7); PTH: parathormone (RV: 12 - 88); AP: alkaline phosphatase (RV < 300).

In the laboratory, the disease is manifested by hypophosphatemia, elevation of plasma alkaline phosphatase concentration, normal serum calcium levels, normal or reduced calciuria, reduced tubular reabsorption of phosphorus and normal plasma concentration of parathyroid hormone[1,9].

Radiological changes are characterized by loss of definition, enlargement and calyx image seen in the provisional calcification zone in the tibial, distal femur, radius and ulna metaphysis[1].

The patient started follow-up at our service late, with significant bone deformities and short stature, in addition to poor treatment compliance. For these reasons, there was no clinical or laboratory improvement in this period.

Burosumab treatment is scheduled to begin, which may reduce the severity of bone deformities and phosphorus elevation, as well as bone pain. The decision to approve this medication for the treatment of X-linked hypophosphatemic rickets in adults and children was based on the results of clinical trials that showed higher serum phosphate levels, aucalcitriol levels, a significant reduction in the severity of rickets, a notable improvement in physical capacity and a significant reduction in pain and functional disability[11,12].

X-linked hypophosphatemic rickets is a rare disease with clinical manifestations that start in the first years of life. Diagnosis and intervention are important for reducing the morbidity and mortality of these patients. Regular follow-up with proper use of medications is essential for the control and reduction of skeletal sequelae.

In patients with clinical, laboratory and radiological findings suggestive of rickets, genetic diagnosis is of fundamental importance, as it can be useful in genetic counseling and in the management of patients with the disease, such as determining the precise treatment.

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