

REVIEW ARTICLE

Hereditary hypophosphatemic ricketsLuis Velásquez-Jones,¹ Mara Medeiros-Domingo²**ABSTRACT**

Hereditary hypophosphatemic rickets (HHR) are a group of diseases characterized by renal phosphate wasting causing growth retardation, rickets and osteomalacia. The most common form is the X-linked dominant hypophosphatemic rickets caused by inactivating mutations in the *PHEX* gene. The other hereditary hypophosphatemic syndromes present a lower prevalence. These include autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets types 1 and 2 and the hereditary hypophosphatemic rickets with hypercalciuria. This article reviews the genetic basis of the different types of HHR, clinical manifestations, biochemical characteristics in blood and urine and new aspects of treatment.

Key words: Hereditary hypophosphatemic rickets; rickets/osteomalacia; hypophosphatemia; phosphate therapy; 1,25-dihydroxyvitamin D3.

INTRODUCTION

The kidney is the most important organ in the regulation of phosphorus balance in the body. Only the ionized form and plasma phosphate complex are ultrafiltrated in the glomerulus. In the renal tubules of the nephron, between ~80 and 97% of the filtered phosphorus is reabsorbed. In the proximal tubule, between 70 and 80% of phosphorus is reabsorbed, 5 to 10% in the distal tubule, and 2 to 3% in the collecting tubules.¹

In the proximal tubule, transport of phosphorus is coupled to that of sodium. In this segment of the nephron, phosphorus transport is mediated by the sodium-phosphate co-transporters. Three sodium-phosphate (NaPi) co-transporters have been described, referred to as type I, type II and type III. Of these, it is considered that the sodium-phosphate co-transporter IIa is the most important because it is responsible for ~70% of the phosphate reabsorption in the

proximal tubule of the nephron.^{1,2} The sodium-phosphate co-transporters take an ion of phosphorus and an anion of sodium. They are released into the cytoplasm of the cells of the proximal tubule of the nephron. Phosphorus then leaves the cell by the action of the Na⁺-K⁺-ATPase pump located at the basolateral portion of the tubular cell.¹

Another important participant in phosphate homeostasis is intestinal absorption. Most ingested phosphorus is absorbed in the duodenum, mainly in the jejunum, through passive diffusion through the paracellular space. When the phosphorus concentration in the intestinal lumen is low, it can be actively absorbed through an intracellular process dependent on type IIb sodium-phosphate co-transporter.^{1,2}

To maintain a neutral balance of phosphate, the amount of phosphate absorbed in the intestine should be similar to the amount excreted, mainly in the urine. This balance is maintained and regulated by the concerted action of different hormones and factors such as parathyroid hormone, fibroblast-23 (FGF-23) growth factor, and the active form of vitamin D, 1 α , 25-dihydroxyvitamin D₃ (1 α ,25(OH)₂D₃).¹

Different pictures of hereditary hypophosphatemias have been described. Each one shows decrease in renal tubular reabsorption of phosphate associated with rickets and osteomalacia.^{1,3} These changes differ among each other based on their mode of hereditary transmission,

¹ Jefe del Departamento de Nefrología
Dr. Gustavo Gordillo Paniagua

² Jefe del Laboratorio de Investigación en Nefrología

Hospital Infantil de México Federico Gómez
México D.F., México

Received for publication: 1-10-13

Accepted for publication: 5-11-13

clinical manifestations, vitamin D metabolism, and treatment response.

The most frequent form of familial hypophosphatemia is inherited as an X-linked dominant trait and is referred to as X-linked hypophosphatemic rickets or X-linked hypophosphatemia (XLH) and comprises almost 80% of cases of hereditary hypophosphatemic rickets. The two forms transmitted by autosomal inheritance include autosomal dominant hypophosphatemic rickets (AEDHR) and autosomal recessive hypophosphatemic rickets (ARHR).³ Finally, the last variant is hereditary hypophosphatemic rickets with hypercalciuria (HHRH), which is inherited as an autosomal dominant trait (Table 1).^{1,3}

X-LINKED HYPOPHOSPHATEMIC RICKETS

Definition

X-linked hypophosphatemic rickets or X-linked hypophosphatemia (XLH) has also received the names of “vitamin D-resistant rickets (VDRR),” “familial hypophosphatemic rickets”, “vitamin D-resistant hypophosphatemic rickets” and “phosphate diabetes.”^{4,5} The term “vitamin D-resistant rickets” should not be used any longer because this disorder is not characterized by vitamin D resistance. An incidence of 1:20,000 has been estimated and, as mentioned, is the most common form of XLH.⁶

Genetics and pathophysiology

XLH is a disorder linked to chromosome X with complete penetration after 1 year of age. The loci of the disease has been located in Xp22.1.⁷ The gene *PHEX* codifies the

production of a protein of 749 amino acids referred to as PHEX (*Phosphate regulating gene with Homologies to Endopeptidases on the X chromosome*).⁸ From its description, different mutations in this gene have been identified in patients with XLH.^{9,10}

The *PHEX* gene codifies a metalloproteinase zinc M13 that is expressed in bones and teeth and, to a lesser degree, in the lung, ovary and testicles but not in the kidney. This gene encodes a peptidase attached to membranes whose substrate is a humoral phosphaturic factor, FGF-23.^{11,12} FGF-23 is mainly produced in bone osteocytes¹³ and induces loss of phosphate in the kidney by suppression of the sodium-phosphate co-transporters type Iia and Iic on the apical surface of the proximal tubule of the nephron, causing development of hyperphosphaturia.¹³⁻¹⁶ Also, FGF-23 induces —through the inhibition of the expression of CYP_{27B}, which encodes the action of the 1- α -hydroxylase—the lesser production of the active metabolite of vitamin D, 1 α ,25(OH)₂D₃, which decreases absorption of phosphate in the intestine and bone.^{13,16-18}

Under normal conditions, PHEX degrades the FGF-23 into inactive fragments, thus avoiding the excessive increase of phosphate excretion and development of hypophosphatemia. However, mutations in PHEX in patients with XLH^{19,20} allow the maintenance of elevated levels of FGF-23. This induces changes of renal tubular absorption of phosphates and development of hypophosphatemia.²¹ It has been recently suggested that the action of the PHEX is carried out through an intermediary metabolite, the extracellular bone matrix protein (ECMP), which controls the circulating levels of FGF-23.³ At the same time, the

Table 1. Hereditary hypophosphatemic rickets: genes, protein mutations and laboratory findings in blood or plasma and urine

	XLH	ADHR	ARHR type 1	ARHR type 2	HHRH
Gene	<i>PHEX</i>	<i>FGF23</i>	<i>DMP1</i>	<i>ENPP1</i>	<i>SLC34A3</i>
Locus	Xp22	12p13	4q22	6q23	9q24
Protein	PHEX	FGF23	DMP1	ENPP1	NaPi-IIc
Phosphate (b)	Low	Low	Low	Low	Low
Calcium (b)	Normal	Normal	Normal	Normal	Normal
1,25(OH) ₂ D ₃	Normal/Low	Normal/Low	Normal/Low	Normal/Low	High
PTH (s)	Normal/High	Normal	Normal/High	Normal	Low
FGF-23 (b)	High/Normal	High/Normal	High/Normal	High/Normal	Normal
Phosphate (u)	High	High	High	High	High
Calcium (u)	Low	Low	Normal/Low	Normal/Low	High

XLH, X-linked hypophosphatemia; ADHR, autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; PTH, parathyroid hormone; b, blood; u, urine.

Modified from Santos² and Bonnardeaux and Bichet.³

action of the FGF-23 is mediated through FGF-23 receptors subtypes 1, 3 and 4 and the transmembranal Klotho co-receptor.^{13,22}

In the disease pathogenesis, a defect is found in the renal tubular reabsorption of phosphate and a lesser production of $1\alpha,25(\text{OH})_2\text{D}_3$ by the kidney. Also, after treatment, secondary hyperparathyroidism can occur and even tertiary in the long term.²³ On the other hand, it has been hypothesized that severe hypophosphatemia induces the development of ricketic lesions by compromising the apoptosis of the hypertrophic chondrocytes in bone growth plate.²⁴

Clinical manifestations

The most common clinical manifestations in XLH are corporal growth delay with low stature. Affected patients usually do not present with hypotonia or weakness, tetany or convulsive crisis, frequent manifestations in children with dependent rickets or vitamin D deficiency.²⁵

The fundamental biochemical alteration, hypophosphatemia, may be present from birth or may develop from 6 to 12 months of age. When hypophosphatemia is present, skeletal growth is delayed and, occasionally, also bone age.⁵ In affected children who develop ricketic lesions, the disease is usually recognized when the child begins to walk; however, if bone radiographic studies are conducted in the first year of life, the initial ricketic lesions can be observed.

As corporal growth progresses in children without treatment, deformities of the lower extremities occur, which include development of *genu valgum* or *genu varum* due to the presence of epiphyseal ricketic lesions in the distal part of the femur and proximal tibia.⁵ In severe cases there may be bone deformities such as *coxa vara* or tibias in shape of a saber. Bone fractures are more common in affected adults.

Usually the length of the chest is normal in children with XLH, so the short stature is mainly due to shortening of the lower extremities.¹⁷ Some patients develop chest deformities, mainly the so-called "pectus carinatum." On the other hand, unlike what is seen in patients with rickets, deficient or dependent on vitamin D, the presentation of costal rosary or upper extremity deformities is rare (Table 2).⁵

Also, patients with severe forms of XLH may present with maxillofacial deformities, with delay in dental development and fractures, abscesses or loss of teeth.

Enlargement of the cavity that contains the pulp is also frequently seen.^{6,26}

Clinical manifestations of rickets are usually less apparent in females than in males of the same family;¹⁷ however, females may also present severe bone deformities. On the other hand, wide variations can be observed in bone compromise and on growth development in members of a family, even of the same gender, despite the presence of comparable degrees of hypophosphatemia.

Laboratory and imaging studies

The basic biochemical alterations in children with XLH consist of the presence of hypophosphatemia, increased alkaline phosphatase, and phosphaturia (Table 3).^{1,5} Variation in age of onset of hypophosphatemia has been observed in patients affected, from the neonatal stage until after 6 months.⁵ Serum alkaline phosphatase levels are elevated, particularly in children with evidence of rickets.

Serum calcium concentration may be normal or mildly reduced. Serum magnesium is usually normal as well as the creatinine concentration in these patients with preserved glomerular filtration.

Parathyroid hormone levels are usually normal. However, some patients may develop secondary or tertiary hyperparathyroidism after long periods of treatment with phosphates.²⁷

The active metabolite levels of vitamin D, $1\alpha,25(\text{OH})_2\text{D}_3$, is usually within normal limits, but these levels are inadequately low in relation with the degree of hypophosphatemia.¹ In some patients low serum levels of $1\alpha,25(\text{OH})_2\text{D}_3$ are found (Table 1).

Table 2. Clinical manifestations in three family members with XLH

	Propositus	Brother	Brother
Age (years)	9	7.5	2.5
Gender	M	M	M
Foot position (age started, months)	9	11	11
Walking (age started, months)	15	14	15
Genu valgum (age started, months)	12	24	4
Pigeon chest	+	-	+
Rachitic rosary	-	±	-

M, male; XLH, X-linked hypophosphatemia.

Rarely has metabolic acidosis been found in some children with XLH, which is corrected with conventional treatment with phosphates and vitamin D. It has been speculated that this transient alteration of the acid-base balance may be caused by a decrease of titratable acid or phosphate depletion, which affects production of adenosine 5-triphosphatase; thus, reabsorption of bicarbonate in the tubule of the nephron.²⁸

Blood findings described contrast with the alterations observed in type 1 vitamin D-dependent rickets and Fanconi syndrome. In the first case, severe hypocalcemia is common with normal or slightly low serum phosphate levels as a consequence of the parathyroid hormone levels; likewise, in these cases serum levels of $1\alpha,25(\text{OH})_2\text{D}_3$ are greatly reduced or undetectable. In cases of children with Fanconi syndrome, severe hypophosphatemia hyperchloremic metabolic acidosis is also found as a result of the accompanying proximal tubular acidosis (Table 4).²⁹

Characteristically, XLH patients have decreased proximal renal tubular reabsorption of phosphate and increased urinary excretion; in addition, maximum tubular transport for phosphate reabsorption is reduced as well as the percentage of tubular phosphate reabsorption.

The normal value of the tubular reabsorption of phosphate (TRP) is >80% and is calculated as follows:

$$\text{TRP} = 1 - [(\text{Up}/\text{Pp}) \times (\text{Pcrea}/\text{Ucrea})]$$

Table 3. Laboratory findings in a 9-year-old child with XLH

	Results	Normal values
Blood		
Hemoglobin (g/dl)	15.7	13-17
CO_2 total (mEq/l)	22.5	22-28
Creatinine (mg/dl)	0.9	0.4-1.0
Calcium (mg/dl)	9.0	8.8-10.8
Phosphate (mg/dl)	2.1	4.5-6.5
ALP (BU)	>33	5-12
Magnesium (mg/dl)	2.1	1.8-3.0
Urine		
pH	5.0	
Density	1.025	
Glucose	Negative	
Calcium (mg/kg/24 h)	0.5	<4
TPR (%)	40	>80

XLHR, X-linked hypophosphatemia; ALP, alkaline phosphatase; TPR, tubular phosphate reabsorption.

where Pp, Up, Pcrea, and Ucrea refer to the concentrations in plasma (P) and urine (U) phosphate (p) and creatinine (create).^{1,28}

The maximum threshold represents the phosphate concentration in the plasma above that which the renal tubular phosphate reabsorption capacity is already saturated. When this last value is linked with the glomerular filtration rate (GFR) it is called "maximum tubular phosphate transport" (TmP/VFG).³⁰ In children between 2 and 15 years of age the normal values of TmP/VFG vary from 3.5-7.5 mg/dl (1.15-2.44 mmol/l).^{1,28} This value is calculated according to the following formula:

$$\text{TmP/GFR} = \text{Pp} - [(\text{Up} \times \text{Pcrea})/\text{Ucrea}]$$

Excretion of calcium via the urine is normal or low in untreated patients. Usually, these patients do not present with aminoaciduria or glycosuria, which allows carrying out the differential diagnosis in patients with Fanconi syndrome who, in addition to severe hypophosphatemia also have the characteristic urinary triad of phosphaturia, glycosuria and aminoaciduria (Table 5).²³

Imaging studies

The finding of rickettic skeletal lesions in children with XLH is common. In severe cases, different degrees of bone demineralization may also be observed. Epiphyseal cartilage calcification defects are detected on x-rays, especially at the distal ends of the long bones.

Remarkably, there is an enlargement of the space between the epiphysis and metaphysis, and the metaphyseal line of calcification has an irregular and "frayed" appearance, forming a "cup" image with concavity towards the epiphyseal side.⁵ Histologically, the skeletal lesion is generalized and is characterized by the presence of increased proportions of unmineralized osteoid (collagen) and defects of mineralization.

Treatment

Because the function of the *PHEX* gene has not been completely elucidated, a specific treatment is not yet available that is aimed at the underlying pathophysiological alterations in this disease. For this reason, current recommended treatment remains the combination of phosphate and $1\alpha,25(\text{OH})_2\text{D}_3$. It has been observed that children who start treatment before 1 year of age have less problems

Table 4. Initial biochemical alterations in blood in three types of rickets of renal origin

Type of rickets	Creatinine	Calcium	Phosphate	AP	Bicarbonate	$1\alpha,25(\text{OH})_2\text{D}_3$	PTH
XLH	N	N	↓↓↓	↑↑↑	N	No ↓	No ↑
Type I VDDR	N	↓↓↓	No ↓	↑↑↑	N	↓↓↓	↑↑↑
FS	No ↑*	No ↓	↓↓↓	↑↑↑	↓↓↓	N	N

AP, alkaline phosphatase; XLH, X-linked hypophosphatemia; VDDR, vitamin D-dependent rickets; FS, Fanconi syndrome; PTH, parathyroid hormone.

N, normal; ↑ and ↑↑↑, increased and highly increased; ↓ and ↓↓↓: decreased and highly decreased.

*In lactating patients with nephrotic cystinosis.

Table 5. Initial biochemical alterations in urine in three types of rickets of renal origin

Type of rickets	Glucose	Aminoacids	Phosphates	Calcium
XLH	N	N	↑↑↑	↓
Type I VDDR	N	No ↑	No ↑*	↓
FS	↑↑↑	↑↑↑	↑↑↑	↑

XLH, X-linked hypophosphatemia; VDDR, vitamin D-dependent rickets; FS, Fanconi syndrome.

N, normal; ↑ and ↑↑↑, increased and highly increased; ↓, decreased.

*Initially as a consequence secondary to hypoparathyroidism.

with growth than those who begin treatment later.³¹ In recent years the usefulness of growth hormones has been suggested in these patients.

The recommended oral phosphate preparation consists of the dissolution of 136 g of dibasic sodium phosphate and 58.5 g phosphoric acid (85% n) in a liter of water. One milliliter of solution contains 30 mg of elemental phosphorus.

The recommended dose of phosphate varies from 30-90 mg/kg/day, with an average of 60 mg/kg/day divided into four doses.^{17,28} Other authors have recommended lower initial doses, 20-40 mg/kg/day.¹⁶ From a practical point of view, if a phosphate solution is used, one can start with 5 ml (150 mg) four times a day (600 mg/day) doses and then increase the dose to 10 ml (300 mg) or 15 ml (450 mg), four times a day² to achieve a total dose of 1-2 g/day.¹ The main problems that arise are the frequency with which the doses should be administered during the day and the diarrhea that develops in the first weeks.⁵ This treatment should be continued until growth has concluded. Subsequently, it should be individualized during adulthood.¹

Is recommended that treatment with phosphate solution be administered simultaneously with $1\alpha,25(\text{OH})_2\text{D}_3$. It is convenient, at the beginning, to start with low doses of active vitamin D and gradually increase the dose. The recommended dose is ~0.02-0.03 µg/kg/day^{16,17,28} which,

for example, in a child weighing 8 kg, means the administration of a second oral dose of 0.25 µg per day.

The use of calcinimetics such as cinacalcet has recently been suggested as adjuvant treatment of patients with XLH.⁶ In eight patients with XLH it was noted that the administration of a phosphate dose induced a transitory increase of serum phosphate, decrease of ionized calcium and elevation of parathyroid hormone levels, whereas the concomitant administration of phosphates and cinacalcet gave as a result a greater reduction of ionized calcium, suppression of parathyroid hormone and increase of serum phosphate.^{2,32}

The concentrations of calcium, phosphate and creatinine in blood, as well as urinary calcium excretion, should be monitored monthly in order to avoid as much as possible the development of hypercalcemia and hypercalciuria.

Early treatment combined with phosphate solution and active vitamin D metabolite allows for improvement in growth speed and biochemical and radiological alterations of rickets. In this regard it has been observed that treated patients have an increase in the mineral volumetric density of trabecular bone in the distal part of the radius, although this volumetric density is smaller in the cortical area of the diaphysis. This probably reflects that the bone mineralization defect is not completely corrected with the currently used treatments.³³ Children presenting with major bone deformities usually require surgical intervention, especially osteotomies in the lower extremities. During treatment with phosphate solution and vitamin D, episodes of hypercalcemia and hypercalciuria may occur; the latter have shown a correlation with the development of nephrocalcinosis in these patients.^{19,28,34} It has also been observed that patients who developed nephrocalcinosis and calcification in cardiac tissues received the highest dose of phosphates and $1\alpha,25(\text{OH})_2\text{D}_3$.^{2,28,35} Therefore, achieving

normal phosphate concentrations in the serum, which are permanent, should not be an obligatory goal of treatment with phosphates. This is also difficult to achieve due to the poor tolerance to its intake because of the risk of the development of hyperparathyroidism and nephrocalcinosis.^{2,16} When a patient develops hypercalciuria (calcium/creatinine ratio in a urine sample >0.3 or >4 mg/kg/24 h on 24 h urine collection) the use of potassium citrate solution has been suggested during treatment because alkalinization of the urine is useful in preventing the precipitation of calcium in the renal tubules.²⁸

An important biomarker of the skeletal response is the activity of alkaline phosphatase in serum. It is found to be moderately elevated before treatment and decreases progressively with treatment and is a useful indicator of improvement of bone lesions.¹⁶

Also, as mentioned, development of tertiary hyperparathyroidism has been described as a complication of the treatment instituted. This has led to the indication of parathyroidectomy in some patients.³⁵⁻³⁷

Failure of the linear growth in children with XLH has been attributed to hypophosphatemia and an alteration in bone metabolism. However, the responsible causes have not been fully defined. It has been proposed that in some patients a deficiency in the production of growth hormone can also occur, thereby worsening its retardation. However, defects in secretion of growth hormone has been proven only in some of the affected patients.²

Treatment with recombinant human growth hormone in patients with XLH is still controversial.^{17,38} In a recent study it was shown that treatment with growth hormone resulted in a sustained increase in linear growth, both in stature in a sitting position as well as the lower extremities without impairment in the proportion between the upper and lower segments of the body.³⁹

Treatment with growth hormone must be evaluated early in the course of the disease after the clinical, biochemical and radiological manifestations of rickets have been controlled, especially in those patients who continue with delay in growth rate or in those who had a delay in the diagnosis of the disease.¹⁷ Haffner et al. reported that administration of growth hormone can lead to a disproportionate growth of the trunk in these patients, which may be considered a negative treatment effect.⁴⁰ In addition, there is the possibility of aggravation of the deformations of the lower extremities.^{2,16}

Recently, studies have been conducted in a hypophosphatemic mouse model in which an inhibitor of the action of the FGF-23 has been used.^{41,42} In these studies it has been demonstrated that treatment for 4 weeks induced increase in body weight, circulating levels of phosphate and of 1,25(OH)₂D₃ in serum and expression of the NaPi-IIa co-transporter in the renal tubule with improvement of bone mineralization evaluated by histomorphometry.⁴¹

Progress and prognosis

The majority of patients maintain an adequate linear height growth when they receive timely treatment with phosphate solution and vitamin D. Early treatment corrects the lower extremity deformities, reduces the number of corrective surgeries, and improves height when adult age is reached.¹⁶ However, it has been noted that many children who already present growth delay at the beginning of treatment, although they later maintain a normal growth rate, do not experience the growth "spurt" that would correct the initial deficit.^{17,38} This supports the concept that the final height of children with XLH depends on the height percentile of the patient at the beginning of treatment.⁴³ Therefore, it is clear that every effort must be made to carry out an early diagnosis so that during the first 2 years of life there is no evident growth delay and the development of skeletal deformities.^{17,28,38}

AUTOSOMAL DOMINANT HYPOPHOSPHATEMIC RICKETS

Autosomal dominant hypophosphatemic rickets (ADHR) is characterized by the presence of renal loss of phosphates with development of persistent hypophosphatemia in families with autosomal dominant inheritance.¹

Genetics and pathophysiology

Family studies have demonstrated that the gene implicated (*FGF23*) is found in the 12p13 chromosome and encodes the production of the FGF-23 peptide.⁴⁴ It has been demonstrated that patients with ADHR have elevated concentrations of FGF-23 related with the presence of severe hypophosphatemia. A concomitant improvement of hypophosphatemia has been observed in patients who during

its evolution demonstrate a reduction of FGF-23 levels.⁴⁴ The mutated circulating FGF-23 shows a more prolonged half-life. Also, fluctuations in serum levels of FGF-23 have been described between normal and elevated values, depending on whether the affected patient has or does not have hypophosphatemia.³

Clinical manifestations

In these families, a variable penetration of the genetic defect has been observed, with some patients who present the phosphate reabsorption defect since childhood and others not until adolescence or adulthood.⁴⁵ Thus, some patients affected with ADHR may have normal phosphate concentrations of FGF-23 in serum during infancy and childhood. This explains the different impact of the disease on body growth in affected families. In these families, some members may not present any growth alterations, and others present a severe delay of body growth.²

Patients who manifest the disease from childhood present rickets and deformities of the lower extremities in a manner similar to that observed in children with XLH. On the other hand, in those whose disease is diagnosed in adulthood there is bone pain, muscle weakness, and some areas of bone fractures, but without lower extremity deformity.^{1,45} In some patients whose clinical manifestations of the disease begin in childhood, disappearance of the defect in the renal tubular reabsorption of phosphate has been observed after puberty.⁴⁵ This indicates that alteration of phosphate metabolism may be compensated by hormonal or other factors not yet recognized.⁴⁶

Laboratory studies

As with patients with XLH, blood studies demonstrated severe hypophosphatemia with reduction of the TRP and TmP/GFR and with normal concentrations of calcium, bicarbonate, creatinine and parathyroid hormone.⁴⁵ The concentration of $1\alpha,25(\text{OH})_2\text{D}_3$ is normal but is also considered to be inadequate for the hypophosphatemia present. Affected patients do not present hypercalciuria, hyperaminoaciduria or glycosuria (Table 1).

Treatment

Treatment for patients with ADHR is similar to that recommended for children with XLH.

AUTOSOMAL RECESSIVE HYPOPHOSPHATEMIC RICKETS

Autosomal recessive hypophosphatemic rickets (ARHR) is a rare form of hereditary hypophosphatemic rickets. Two variants have been recognized and referred to as type 1 and type 2.^{2,6,47}

Genetics

Type 1 ARHR is caused by inactivating mutations of the *DMP1* gene located on chromosome 4q22, which encodes the protein DMP1 (dentin matrix protein-1). These give as a result the secondary elevation of serum levels of FGF-23.² The DMP1 protein is mainly expressed in cellular lines of osteoblasts and osteocytes.³

Type 2 ARHR is developed due to mutations of *ENPP1* gene located on chromosome 6q23, which encodes the ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*).^{2,6,16}

Clinical manifestations

Bone alterations do not usually arise from birth but during childhood and even during adult age.³ In a manner similar to ADHR, affected patients may have normal growth, whereas others develop important bone deformities (*genu valgum*) and severe body growth delay.²

Laboratory studies

Blood alterations are similar to those observed in patients with XLH. Hypophosphatemia, normocalcemia, elevated levels of alkaline phosphatase, normal or elevated levels of FGF-23 and normal or inadequately low levels of $1\alpha,25(\text{OH})_2\text{D}_3$ are observed.^{2,3,6} In the urine, in addition to hyperphosphatemia, decreased or normal calcium excretion may be observed (Table 1).²

Treatment

Treatment is similar to that indicated in patients with XLH.

HEREDITARY HYPOPHOSPHATEMIC RICKETS WITH HYPERCALCIURIA

Only sporadic cases of patients with hereditary hypophosphatemic rickets with hypercalciuria (HHRH) have been described.⁴⁸⁻⁵³ The disease was initially described in a population of Bedouins with high rates of consanguin-

ity.^{4,48,54} This type of inheritance has been defined as the autosomal recessive variant.^{3,53}

Genetics

It has been shown that the HHRH is caused by a biallelic mutation in the *SLC34A3* gene located on chromosome 9q34,⁵⁴ which encodes for type IIc sodium-phosphate co-transporter (NaPi-IIc) in the proximal tubule of the nephron.^{3,55,56} Apparently, these patients probably share the same genetic defect as patients with idiopathic hypercalcuria because both disorders have been found in members of the same family.¹

Pathogenesis

In contrast to cases of XLH and ADHR, patients with HHRH respond adequately to hypophosphatemia with increased levels of $1\alpha,25(\text{OH})_2\text{D}_3$ in response to stimulation of the 1α -hydroxylase enzyme. Elevation of the levels of $1\alpha,25(\text{OH})_2\text{D}_3$ induces greater absorption of calcium and phosphate from the gastrointestinal tract and suppression of parathyroid hormone secretion. In addition, hypercalciuria occurs as a result of the high levels of the active metabolite of vitamin D.⁵⁴

Clinical manifestations

The main clinical manifestations of HHRH include bone pain, skeletal deformities, low stature and muscular weakness.⁵⁴ When the disease occurs during infancy or childhood, radiological changes of rickets are evident.⁴⁸ Serum levels of FGF-23 are not elevated in patients with HHRH, which highlights the important role of hypophosphatemia as a cause of growth delay.²

Laboratory studies

Blood biochemical alterations of HHRH include hypophosphatemia, normal concentrations of calcium, increased alkaline phosphatase, decreased parathyroid hormone values and high concentrations of $1\alpha,25(\text{OH})_2\text{D}_3$.⁵³ Serum levels of FGF-23 are usually normal, although they may be elevated.⁵⁶

In the urine, renal phosphate loss is demonstrated with reduction of the TRP and of the TmP/GFR. Elevation of the serum levels of the $1\alpha,25(\text{OH})_2\text{D}_3$ is associated with a significant increase in the excretion of calcium in the urine (Table 1).⁵³ Affected patients may develop recurrent renal lithiasis and nephrocalcinosis.^{53,57}

Treatment

Administration of the phosphate solution in patients with HHRH induced improvements in growth, disappearance of bone pain, muscular weakness and radiological signs of rickets. Plasma phosphate concentration increased and reduction of serum alkaline phosphatase and of $1\alpha,25(\text{OH})_2\text{D}_3$ was observed. On the other hand, there is decrease in urinary calcium excretion, although the TRP and TmP/GFR are unchanged.¹ In these patients, administration of $1\alpha,25(\text{OH})_2\text{D}_3$ is not recommended.⁵³

Correspondence: Dr. Luis Velásquez-Jones
E-mail: velasquezjones@hotmail.com

REFERENCES

- Velásquez JL. Alteraciones Hidroelectrolíticas en Pediatría. México: Editorial Prado; 2010. p. 328.
- Santos F, Fuente R, Mejía N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol* 2013;28:595-603.
- Bonardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, eds. *Brenner and Rector's The Kidney*. Philadelphia: Elsevier Saunders; 2012. pp. 1584-1625.
- Tenenhouse HS, Econis MJ. Mendelian hypophosphatemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Diseases*. New York: McGraw-Hill; 2001. pp. 5039-5967.
- Velásquez JL, Dorantes AL, Ajuria ML. Raquitismo hipofosfatómico resistente a la vitamina D. *Bol Med Hosp Infant Mex* 1984;41:561-568.
- Gattineni J, Baum M. Genetic disorders of phosphate regulation. *Pediatr Nephrol* 2012;27:1477-1487.
- Mächler M, Frey D, Gal A, Orth U, Wienker TF, Fanconi A, et al. X-linked dominant hypophosphatemia is closely linked to DNA markers DDXS41 and DDXS43 at Xp22. *Hum Genet* 1986;73:271-275.
- The HYP Consortium. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. *Nat Genet* 1995;11:130-136.
- Durmaz E, Zou M, Al-Rijjal RA, Baitel EY, Hammami S, Bircan I, et al. Novel and de novo PHEX mutations in patients with hypophosphatemic rickets. *Bone* 2010;52:286-291.
- Morey M, Castro-Feijoó L, Barreiro J, Cabanas P, Pombo M, Gil M, et al. Genetic diagnosis of X-linked dominant hypophosphatemic rickets in a cohort study: tubular reabsorption of phosphate and $1,25(\text{OH})_2\text{D}$ serum levels associated with PHEX mutation type. *BMC Med Genet* 2011;12:116.
- Schiavi CS, Kumar R. The phosphatonin pathway: new insights in phosphate homeostasis. *Kidney Int* 2004;65:1-14.
- Takeda E, Taketani Y, Sawada N, Sato T, Yamamoto H. The regulation and function of phosphate in the human body. *Biofactors* 2004;21:345-355.

13. Bonewald LF, Wacker MJ. FGF23 production by osteocytes. *Pediatr Nephrol* 2013;28:563-568.
14. Safirstein R. Vitamin D receptor in bone regulates osteoclastogenesis, FGF23 production, and phosphate homeostasis. *Kidney Int* 2007;71:289.
15. Forster IC, Hernando N, Biber J, Murer H. Proximal tubular handling of phosphate: a molecular perspective. *Kidney Int* 2006;70:1548-1559.
16. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res* 2011;26:1381-1388.
17. Ariceta G, Langman CB. Growth in X-linked hypophosphatemic rickets. *Eur J Pediatr* 2007;166:303-309.
18. Liu S, Gupta A, Quarles LD. Emerging role of fibroblast growth factor 23 in a bone-kidney axis regulating systemic phosphate homeostasis and extracellular matrix mineralization. *Curr Opin Nephrol Hypertens* 2007;16:329-335.
19. Cho HY, Lee BH, Kang JH, Ha ILS, Cheong HI, Choi Y. A clinical and molecular genetic study of hypophosphatemic rickets in children. *Pediatr Res* 2005;58:329-333.
20. Roetzer KM, Varga F, Zwettler E, Nawrot-Wawrzyniak K, Haller J, Foster E, et al. Novel PHEX mutation associated with hypophosphatemic rickets. *Nephron Physiol* 2007;106:8-12.
21. Quarles LD. FGF23, PHEX, and MEPE regulation of phosphate homeostasis and skeletal mineralization. *Am J Physiol Endocrinol Metab* 2003;285:E1-E9.
22. Gattineni J, Baum M. Regulation of phosphate transport by fibroblast growth factor 23 (FGF23): implications for disorders of phosphate metabolism. *Pediatr Nephrol* 2010;25:591-601.
23. Schmitt CP, Mehls O. The enigma of hyperparathyroidism in hypophosphatemic rickets. *Pediatr Nephrol* 2004;19:473-477.
24. Demay MB, Sabbagh Y, Carpenter TO. Calcium and vitamin D: what is known about the effects on growing bone. *Pediatrics* 2007;119:S141-S144.
25. Velásquez JL, Gordillo PG. Raquitismo dependiente de vitamina D tipo I: tratamiento con 1,25-dihidroxivitamina D. *Bol Med Hosp Infant Mex* 1984;41:36-40.
26. Pereira CM, de Andrade CR, Vargas PA, Coletta RD, de Almeida OP, Lopes MA. Dental alterations associated with X-linked hypophosphatemic rickets. *J Endod* 2004;30:241-245.
27. Mäkitie O, Kooh SW, Sochett E. Prolonged high-dose phosphate treatment: a risk factor for tertiary hyperparathyroidism in X-linked hypophosphatemic rickets. *Clin Endocrinol (Oxf)* 2003;58:163-168.
28. Vaisbuch MH, Koch VH. Hypophosphatemic rickets: results of a long-term follow-up. *Pediatr Nephrol* 2006;21:230-234.
29. Velásquez JL. Raquitismo de origen renal. In: Meneghelli RJ, ed. *Diálogos en Pediatría*. Santiago de Chile: Mediterráneo; 1995. pp. 225-230.
30. Mota HF, Velásquez JL. *Trastornos Clínicos de Agua y Electrólitos*. México: McGraw-Hill Interamericana; 2004. p. 143.
31. Quinlan C, Guegan K, Offiah A, O'Neill R, Hiorns MP, Elillard S, et al. Growth in PHEX-associated X-linked hypophosphatemic rickets: the importance of early treatment. *Pediatr Nephrol* 2012;27:581-588.
32. Alon US, Levy-Olomucki R, Moore WV, Stubbs J, Liu S, Quarles LD. Calcimimetics as an adjuvant treatment for familial hypophosphatemic rickets. *Clin J Am Soc Nephrol* 2008;3:658-664.
33. Cheung M, Roschger P, Klaushofer K, Veilleux LN, Roughley P, Glorieux FH, et al. Cortical and trabecular bone density in X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab* 2013;98:E954-E961.
34. Bacchetta J, Salusky IB. Evaluation of hypophosphatemia: lessons from patients with genetic disorders. *Am J Kidney Dis* 2012;59:152-159.
35. Sun GE, Suer O, Carpenter TO, Tan CD, Li-Ng M. Heart failure in hypophosphatemic rickets: complications from high-dose phosphate therapy. *Endocr Pract* 2013;19:e8-e11.
36. McHenry CR, Mostafavi K, Murphy TA. Tertiary hyperparathyroidism attributable to long-term oral phosphate therapy. *Endocr Pract* 2006;12:294-298.
37. Savio RM, Gosnell JE, Posen S, Reeve TS, Delbridge LW. Parathyroidectomy for tertiary hyperparathyroidism associated with X-linked dominant hypophosphatemic rickets. *Arch Surg* 2004;139:218-222.
38. Mäkitie O, Doria A, Kooh SW, Cole WG, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab* 2003;88:3591-3597.
39. Zivcicjak M, Schnabel D, Staude H, Even G, Marx M, Beetz R, et al; Hypophosphatemic Rickets Study Group of the Arbeitsgemeinschaft für Pädiatrische Endokrinologie und Gesellschaft für Pädiatrische Nephrologie. Three-year growth hormone treatment in short children with X-linked hypophosphatemic rickets: effects on linear growth and body disproportion. *J Clin Endocrinol Metab* 2011;96:E2097-E2105.
40. Haffner D, Nissel R, Wühl E, Mehls O. Effects of growth hormone treatment on body proportions and final height among small children with X-linked hypophosphatemic rickets. *Pediatrics* 2004;113:e593-e596.
41. Zhang MY, Ranch D, Pereira RC, Armbrecht HJ, Portale AA, Perward F. Chronic inhibition of ERK1/2 signaling improves disordered bone and mineral metabolism in hypophosphatemic (Hyp) mice. *Endocrinology* 2012;153:1806-1816.
42. Wöhrl S, Henninger C, Bonny O, Thüery A, Beluch N, Hynes NE, et al. Pharmacological inhibition of fibroblast growth factor (FGF) receptor signaling ameliorates FGF23-mediated hypophosphatemic rickets. *J Bone Miner Res* 2013;28:899-911.
43. Baroncelli GI, Bertelloni S, Ceccarelli C, Saggese G. Effect of growth hormone treatment on final height, phosphate metabolism, and bone mineral density in children with X-linked hypophosphatemic rickets. *J Pediatr* 2001;138:236-243.
44. Imel EA, Hui SL, Econis MJ. FGF23 concentrations vary with the disease status in autosomal dominant hypophosphatemic rickets. *J Bone Miner Res* 2007;22:520-526.
45. Econis MJ, McEnery PT. Autosomal dominant hypophosphatemic rickets/osteomalacia: clinical characterization of a novel renal phosphate-wasting disorder. *J Clin Endocrinol Metab* 1997;82:674-681.
46. Kruse K, Woelfel D, Strom TM. Loss of renal phosphate wasting in a child with autosomal dominant hypophosphatemic rickets caused by a FGF23 mutation. *Horm Res* 2001;55:305-308.
47. Prié D, Friedlander G. Genetic disorders of renal phosphate transport. *N Engl J Med* 2010;362:2399-2409.
48. Tieder M, Modai D, Samuel R, Arie R, Halabe A, Bab I, et al. Hereditary hypophosphatemic rickets with hypercalciuria. *N Engl J Med* 1985;32:611-617.
49. Proesmans WC, Fabrey G, Marchal GJ, Gillis PL, Bouillon R. Autosomal dominant hypophosphataemia with elevated serum 1,25-dihydroxyvitamin D and hypercalciuria. *Pediatr Nephrol* 1987;1:479-484.

50. Chen C, Carpenter T, Steg N, Baron R, Anast C. Hypercalciumic hypophosphatemic rickets, mineral balance, bone histomorphometry, and therapeutic implications of hypercalcioria. *Pediatrics* 1989;84:276-280.
51. Tieder M, Arie R, Bab I, Maor J, Liberman UA. A new kindred with hereditary hypophosphatemic rickets with hypercalcioria: implications for correct diagnosis and treatment. *Nephron* 1992;62:176-181.
52. Tieder M, Modai D, Shaked U, Samuel R, Arie R, Halabe A, et al. "Idiopathic" hypercalciuria and hereditary hypophosphatemic rickets. Two phenotypical expressions of a common genetic defect. *N Engl J Med* 1987;316:125-129.
53. Areses-Trapote R, López-García JA, Ubetagoyena-Arrieta M, Eizaguirre A, Sáez-Villaverde R. Hereditary hypophosphatemic rickets with hypercalcioria: case report. *Nefrologia* 2012;32:529-534.
54. Bergwitz C, Roslin NM, Tieder M, Loredo-Osti JC, Bastepe M, Abu-Zahra A, et al. SCL34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalcioria predict a key role for the sodium-phosphate cotransporter NaPi-IIc in maintaining phosphate homeostasis. *Am J Hum Genet* 2006;78:179-192.
55. Ichikawa S, Sorenson AH, Imel EA, Friedman NE, Gertner JM, Econo MJ. Intronic deletions in the SLC34A3 gene cause hereditary hypophosphatemic rickets with hypercalcioria. *J Clin Endocrinol Metab* 2006;91:4022-4027.
56. Braithwaite V, Pettifor JM, Prentice A. Novel SLC34A3 mutation causing hereditary hypophosphataemic rickets with hypercalcioria in a Gambian family. *Bone* 2013;53:216-220.
57. Kremke B, Bergwitz C, Ahrens W, Schütt S, Schumacher M, Wagner V, et al. Hypophosphatemic rickets with hypercalcioria due to mutation of SLC34A3/NaPi-IIc can be masked by vitamin D deficiency and can be associated with renal calcifications. *Exp Clin Endocrinol Diabetes* 2009;117:49-56.