

# Hereditary hypophosphataemic rickets: experience from a paediatric nephrology unit

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## ■ ABSTRACT

**Introduction.** Rickets is a paediatric disease which should be suspected in children presenting with failure to thrive, motor developmental delay and orthopaedic abnormalities. Although rare, hereditary hypophosphataemic rickets is the most common form of heritable rickets.

**Patients and Methods.** Retrospective observational study of all children with hypophosphataemic rickets observed at a paediatric nephrology unit of a tertiary paediatric hospital from 1982 to 2012, identified from the unit's database. Data collected included demographics, risk factors, pre-existing medical conditions, clinical, radiographic and laboratory findings, treatment and morbidity.

**Results.** Eleven children with hypophosphataemic rickets were studied, with a median age at admission of 4.25 years (0.66-10.92). Family history of rickets or orthopaedic abnormalities was found in five children. The first clinical manifestations were delayed/abnormal gait (7/11) and short stature (4/11). Skeletal deformities were present in all children: genu valgum or varum (11/11), thickening of the wrists (7/11), rachitic rosary (4/11), frontal skull bossing (2/11), Harrison's groove (1/11). Dental abscess was reported in one child and joint pain in six. Laboratory findings included increased alkaline phosphatase (11/11), low serum phosphorus (11/11), normal serum calcium (10/11) and parathyroid hormone values (6/11) and low renal phosphorus reabsorption rate (9/10). None of the

children had hypercalciuria. All children were treated with oral phosphorus and calcitriol (8/11 with lack of compliance). Seven children were discharged with a median age of 16.5 years; all had bone deformities, 5/7 had short stature and 1/7 had nephrocalcinosis.

**Discussion.** Hypophosphataemic rickets is a rare disease with significant long-term morbidity. It should be suspected in children presenting with short stature, developmental delay and orthopaedic abnormalities. Increased alkaline phosphatase, low serum phosphorus with normal serum calcium and impaired renal tubular reabsorption of phosphate confirm the diagnosis. Early diagnosis and treatment are essential to minimise morbidity in children.

### Key-Words:

Children; hereditary hypophosphataemic; rickets.

## ■ INTRODUCTION

Rickets is a disease of children and adolescents, caused by a failure of growing bone to mineralise. When this happens in adults after growth-plates fusion, it is called osteomalacia<sup>1</sup>. Rickets is "not a disease only of the past, nor is it limited to developing countries"<sup>2</sup>. Although nutritional rickets from vitamin D deficiency is the most common type of this disease, there are several other forms, unrelated to diet or sunlight exposure<sup>1,3</sup> (Table I). In the United States, between 1986 and 2000 less than one-third

**Table I**

Types of Rickets

Calcipaeic Rickets ↑ AF, ↓ Ca, N/↓ Pi, ↑ PTH	Causes	Biochemical findings
<b>Nutritional</b> – Vitamin D deficiency – Calcium deficiency – Malabsorption syndromes	Low diet intake Low sunlight exposure IBD, celiac disease, cystic fibrosis, gastrectomy Hepatic disease, chronic renal disease	↓ 25(OH)D
<b>Genetic</b> Vitamin D dependent – Type I or Pseudovitamin D deficiency rickets – Type II or Vitamin D resistant rickets	– 1 $\alpha$ -hydroxylase deficiency (defective conversion of 25(OH)D to 1,25(OH) <sub>2</sub> D – Dysfunction of vitamin D receptors (organ resistance)	N 25(OH)D ↓ 1,25(OH) <sub>2</sub> D N 25(OH)D ↑↑ 1,25(OH) <sub>2</sub> D
<b>Drugs</b>	Anticonvulsants (fenobarbital, hydantoin), loop diuretics, corticosteroids, colestyramine	
Phosphopaenic Rickets ↑ AF, N Ca, ↓ Pi, N PTH		
<b>Genetic</b> ↑ FGF-23action: Hereditary hypophosphataemic rickets (X-linked, AD, AR)	Impaired proximal renal tubular reabsorption of Pi and inappropriately normal calcitriol levels	N 25(OH)D N/↓ 1,25(OH) <sub>2</sub> D ↓ Ca(u)
↓ FGF-23action: Hereditary hypophosphataemic rickets with hypercalciuria	Impaired proximal renal tubular reabsorption of Pi and increased calcitriol	N 25(OH)D ↑ 1,25(OH) <sub>2</sub> D ↑ Ca(u)
<b>Diseases with phosphaturia</b> FGF-23 independent FGF-23 dependent	Fanconi syndrome, Dent's disease, tubular disease Tumour-induced inhibition of renal 25(OH)D <sub>3</sub> -1 $\alpha$ -hydroxylase	↓ 1,25(OH) <sub>2</sub> D
<b>Drugs</b>	Corticosteroids, aluminium hydroxide	
Others		
<b>Renal osteodystrophy</b>	Loss of functional renal parenchyma leads to mineral derangements and decreased calcitriol production	↓ 25(OH)D ↓ 1,25(OH) <sub>2</sub> D

AF = alkaline phosphatase; Ca = serum calcium; Pi = serum phosphates; N = normal; PTH = parathyroid hormone; IBD= inflammatory bowel disease; 25(OH)D = Calcidiol; 1,25(OH)<sub>2</sub>D = Calcitriol; AD = Autosomal dominant; AR = Autosomal recessive; FGF-23 = Fibroblast growth factor; Ca(u) = Calciuria

of children with rickets had nutritional deficiencies, with genetic factors or underlying diseases remaining as the main factors responsible for the illness<sup>2</sup>. Nowadays the incidence of rickets is not known with accuracy, since there is no national surveillance.

Rickets should be suspected in children presenting with failure to thrive, developmental delay and orthopaedic abnormalities (with asymmetry, pain, or progression in severity). Skeletal changes occur because of the lack of calcified osteoid and the build-up of unossified cartilage<sup>1</sup>. These are confirmed by characteristic radiographic signs (Table II)<sup>2-6</sup>.

Rickets can be classified into two major groups: calcipaeic and phosphopaenic rickets. While the skeletal findings are similar for both, the extraskelatal manifestations of rickets vary depending upon the

primary mineral deficiency (hypoplasia of the dental enamel is typical of calcipaeic rickets, whereas dental abscesses are frequent in phosphopaenic rickets). Serum phosphorus usually is low in phosphopaenic rickets while serum calcium is normal, and may be

**Table II**

Characteristic Skeletal and Radiographic Findings of Rickets

- Delayed closure of anterior fontanel
- Frontal bossing of skull
- Craniotabes (soft skull bones)
- Costochondral beading (rachitic rosary)
- Flaring of ribs at diaphragm level (Harrison's groove)
- Widening of the wrist and bowing of distal radius and ulna
- Genu valgum or varum
- Osteopaenia
- Fractures

either decreased or normal in calcipenic rickets, along with typically elevated parathyroid hormone (PTH). Serum concentrations of 25-OH vitamin D (calcidiol) are low in vitamin D deficiency.

Most of the hypophosphataemic disorders are inherited<sup>2,3</sup>, including X-linked (XLH), autosomal dominant (ADHR) and autosomal recessive rickets (ARHR) and hypophosphataemic rickets with hypercalciuria. Hereditary hypophosphataemic rickets is a rare form of disease, with the most common X-linked. It results from a reduction in the phosphate reabsorption by the renal tubuli, which leads to chronic hyperphosphaturia and hypophosphataemia<sup>1,2,6</sup>. The tubular maximum reabsorption of phosphate estimates the renal phosphate loss<sup>3</sup>. There is also a decreased synthesis of calcitriol. Early treatment with phosphate and calcitriol can optimise height outcome and improve the rickets.

Hypophosphataemic rickets with hypercalciuria (HRH) is another rare form of disease, with autosomal recessive heredity. It is distinguished by an increased urinary calcium excretion and elevated plasma calcitriol. Because HRH is treated with phosphorus supplementation alone, plasma calcitriol levels and urinary calcium excretion must be measured in every patient with phosphopaenic rickets before initiating therapy.

Fibroblast-growth factor 23 (FGF23), a circulating hormone that causes renal phosphate wasting, is increased in XLH rickets, ADHR and ARHR and decreased in HRH.

Tumour-induced osteomalacia (TIO) is an acquired disorder, with many features in common with familial syndromes. It should be considered if the onset of phosphate wasting presents later in childhood or adolescence.

This study intended to characterise the population of children with hypophosphataemic rickets observed over the last 31 years at our unit.

## ■ PATIENTS AND METHODS

A retrospective observational study of all children with hypophosphataemic rickets was performed at

the paediatric nephrology unit of a tertiary paediatric hospital. Children selected were observed at this unit in a period of 31 years from the year 1982 to 2012.

Patients were identified from the unit's database, including IT and paper registries. Data collected included demographics, height at birth, height and year of first consultation; diet content in calcium and vitamin D, sunlight exposure, pre-existing medical conditions, previous medications; skeletal, extraskel-etal and radiographic findings; laboratory results (alkaline phosphatase, serum calcium and phosphorus, parathyroid hormone, calcidiol (25-OH vitamin D), renal phosphorus reabsorption rate) at diagnosis and evolution; treatment and morbidities; age at discharge. Alkaline phosphatase values were all determined at the same laboratory and normal range was adjusted for children's age and sex. Stature was evaluated according to 2000 CDC Growth Charts for the United States.

## ■ RESULTS

There were 11 children with hypophosphataemic rickets (Table III). Six were diagnosed in the last 12 years and nine were girls. The median age at admission was 4.25 years, varying from ten months to 10.9 years, and the follow-up time had a median of 8.33 years (2.67 to 18.08 years).

Low sunlight exposure was reported in only one child and lack of vitamin D supplementation in two. Malabsorption disease and pharmacological habits were not found. Family history of rickets or orthopaedic abnormalities was found in five children (four in a first-degree relative).

The first clinical manifestations were delayed/abnormal walk (seven children) and short stature, present in four children. Of these, one had failure to thrive and another had delayed dental eruption. Skeletal deformities were present in all children: genu valgum or varum (11/11), thickening of the wrists (7/11), rachitic rosary (4/11), frontal bossing of skull (2/11), Harrison's groove (1/11). Dental abscess was reported in one child and joint pain in six.

At admission all children's height was below the 5<sup>th</sup> centile (adjusted for age and gender). Laboratory

Table III

Hypophosphataemic Rickets in the Paediatric Nephrology Unit

	Gender	Age (Y) at diagnosis	Year	Family history	Complications		
					SS	BD	NC
1	F	0.84	1982	–	√	√*	–
2	F	11	1984	–	√	√*	–
3	F	1.42	1985	Father	√	√*	–
4	M	5.75	1995	Mother	–	√*	–
5	F	4.25	1998	Mother	√	√*	√
6	M	7.08	2000	–	–	√	–
7	F	2.25	2002	–	√	√	–
8	F	10.92	2003	–	√	√	–
9	F	3	2004	Mother	√	√	–
10	F	2.75	2004	Grandmother	√	√	–
11	F	4.25	2009	–	√	√	–

F = Female; M = Male; SS = Short stature; BD = Bone deformities; NC = Nephrocalcinosis; √ = Present; – = Not present; \* = Orthopaedic surgery. None of the patients had tertiary hyperparathyroidism.

findings included increased alkaline phosphatase (11/11), median of 400 UI/L (192-665); low serum phosphorus (11/11), with a median of 0.8 mmol/L (0.59-1); serum calcium within the normal range (10/11), median of 2.23 mmol/L (1.8-2.25); normal parathyroid hormone values in six children, increased in five; low renal phosphorus reabsorption rate (9/10), median of 72% (50-83); calcidiol levels available were within the normal range (4/4) and none of the children had hypercalciuria.

The biochemical characteristics were collected for every year of follow-up. Phosphate levels were always low. Calciuria was determined from 24-hours urine at the initial study and posterior values were obtained by calcium/creatinine ratio. Only three children had elevated values, all with lack of compliance: two had hypercalciuria at the last observation and emigrated with their families; one girl had transient elevated calciuria and is now controlled. At the beginning of the study there were few results of PTH, which were available with regular basis only from 1992 forth. The large majority of these values were elevated.

All children were treated with four or five daily doses of oral phosphorus and calcitriol. Calcitriol dose varied from 10 to 20 ng/kg/dose, twice a day. Phosphorus was prescribed to achieve 40 mg/kg/day, divided in four or five doses.

Therapy was adjusted to minimise gastrointestinal side effects (diarrhoea) and adjust serum phosphate

levels, calciuria and parathyroid hormone. Lack of compliance or irregular medication was reported in eight children, in all cases associated with phosphorus administration.

Seven children, with a median age of 16.5 years, were discharged and transferred to adult medical care. Most of them had short stature: final stature below the 3<sup>rd</sup> centile (5/7), in the 5<sup>th</sup> centile (1/7) and in the 10<sup>th</sup> centile (1/7). Bone deformities of legs persisted in all children and 5/7 were submitted to at least one orthopaedic surgery correction during follow-up. All children were performing renal ultrasonography and there was one case of nephrocalcinosis. The girl with nephrocalcinosis (stage I bilateral renal echogenicity) was followed from 4 to 17 years old. She did not have hypercalciuria but PTH values were higher than other children (range from 80 to 394 pg/mL). Calcitriol dose was similar. None had tertiary hyperparathyroidism. In three cases the diagnosis of hypophosphataemic X-linked rickets was confirmed by genetic studies.

## DISCUSSION

Hypophosphataemic rickets (HR) is a rare genetic disease, due to increased action of FGF23, a hormone-like substance secreted by the osteoblasts, active in renal tubuli, that promotes hypophosphataemia by decreasing the renal phosphorus reabsorption<sup>1,3</sup>.

Recent experiments suggest that primary action of FGF23 is on vitamin D metabolism, and the effects on phosphate could be secondary (independent of PTH). FGF23 acts on renal phosphate transport indirectly by influencing vitamin D metabolism and suppressing serum levels of 1,25-vitamin D<sub>3</sub> (due to a suppression of the anabolic 25-hydroxyvitamin D<sub>3</sub>-1(alpha)-hydroxylase (1 $\alpha$ -hydroxylase) and an increase in expression of the catabolic 24-hydroxylase)<sup>3,7-11</sup>.

PHEX (Phosphate-regulating gene with Homologies to Endopeptidases on the X-chromosome) also plays a major role in renal phosphate handling. It is expressed predominantly in bones and teeth (osteoblasts and odontoblasts) but not expressed in the kidney, which suggests the secondary involvement of a circulating systemic factor. Loss of PHEX function indirectly results in the secretion of specific factors by the osteoblast (phosphatonins, that inhibit renal phosphate handling, and minhibins that inhibit mineralisation). Although physiological substrate for PHEX remains elusive, peptides of FGF23 and MEPE (Matrix Extracellular Phosphoglycoprotein, a protein that inhibits phosphate-uptake and mineralisation) were proposed<sup>8</sup>.

The pathogenesis of hypophosphataemic rickets is not fully understood. Increased levels of FGF23 appear to be an important common pathway for hereditary hypophosphataemic rickets and TIO, but the mechanisms for the increased FGF23 vary among these disorders. In XLH rickets, the primary defect is a defective Znmetalloendopeptidase called PHEX, resulting in increased full-length FGF23 and MEPE expression. This causes defects in mineralisation, leading to rickets, dental abnormalities, and/or osteomalacia. The other clinical manifestations of XLH rickets (such as enthesiopathy and dental abnormalities) may also be mediated by mechanisms other than FGF23. In ADHR, activating mutations in FGF23 gene result in proteins resistant to protease cleavage by PHEX or other proteases, and so circulating levels of FGF23 are increased, with consequently inhibition of renal phosphate reabsorption<sup>8,9</sup>. In TIO, the tumours (typically benign, small and of mesenchymal origin) are the responsible for the production of the phosphaturic hormone (FGF23)<sup>8</sup>. ARHR is caused by inactivating mutations in the DMP1 gene, which encodes Dentin matrix protein 1 and results in increased FGF23 expression and defective osteocyte maturation.

In this study there were only 11 children over 31 years of study, reflecting the rarity of the disease. In literature, there was no gender predominance (mostly X-linked dominant hereditarily)<sup>12-14</sup> but we report a female predominance (9/11).

The medical history of any child with rickets should include infant's gestational age, a detailed dietary history (calcium and vitamin D), the amount of sunlight exposure, medical conditions (malabsorption syndromes, renal disease, malignancy) and medications associated with rickets (loop diuretics, corticosteroids, anticonvulsants and antacids)<sup>2,4,5</sup>.

Children with HR are usually born with normal length. Since there is an adequate growth velocity in the first years of life, the first clinical manifestations result from the period of slow-growth velocity before diagnosis is made<sup>1,2</sup>. Skeletal abnormalities appear later in life, with weight bearing after starting to walk, and are less pronounced than in vitamin D deficiency rickets<sup>15,16</sup>. Family history may allow an earlier diagnosis, around the 6<sup>th</sup> month of life. In this study the median age at admission was 4.25 years and all children had skeletal abnormalities. The youngest child's mother had diagnosed disease, and the oldest had been followed in several units for short stature and had no family history.

When there is no family history, the diagnosis of rickets in children with compatible clinical and laboratory findings should exclude other diseases that also cause rickets, hypophosphataemia and reduced renal phosphorus reabsorption rate (Hereditary hypophosphataemic rickets with hypercalciuria, Fanconi syndrome, Dent's disease, malabsorption syndromes, malignancy).

The evaluation of a child with clinical signs of rickets should include measurement of serum creatinine and liver enzymes to exclude renal insufficiency as the primary aetiology or liver disease as the cause of elevated serum alkaline phosphatase activity. Serum phosphorus and PTH measurements allow the diagnosis of rickets and determine the initial classification of the disease.

Laboratory investigation may include alkaline phosphatase<sup>17</sup>, serum levels of calcium (total and

ionised with serum albumin), phosphorus, parathyroid hormone, urea nitrogen, creatinine, calcidiol and levels of urinary calcium and phosphorus. Serum levels of 1,25 OH<sub>2</sub> vitamin D are not stable and should not be used to diagnose vitamin D deficiency or insufficiency.

The characteristic findings in HR are increased alkaline phosphatase, hypophosphataemia, decreased renal phosphorus reabsorption rate and a normal or increased parathyroid hormone, with the remaining values within the normal range. However, laboratory values can vary depending on the stage of the disease and previous medication, which explains the different results in our study.

Genetic studies are the most recent tool to diagnose rickets (the majority of patients with XLH rickets are caused by PHEX mutations; singular cases have been reported with mutations in FGF23, DMP1 and ENPP1)<sup>9</sup>. Although very helpful confirming the disease, they are expensive and not easily available worldwide (three of our cases were confirmed to be hypophosphataemic X-linked rickets, due to mutations on PHEX gene (Xp22.1))<sup>12,14</sup>.

The measurement of serum FGF23 levels is a promising laboratory examination<sup>18-20</sup>. In chronic kidney disease, phosphate levels rise with declining glomerular filtration rate and increase FGF23 levels, to promote renal phosphate excretion; pretreatment circulating FGF23 levels may allow us to predict the refractoriness to calcitriol therapy and increased FGF23 levels are associated with increasing risk of mortality in dialysis patients. In oncogenic osteomalacia, FGF23 is elevated in preoperative serum of patients and normalises after resection of the causative tumor. FGF23 could be also appropriated for the first screening step in determining the etiology of FGF23-related hypophosphataemic rickets. As such, FGF23 appears to be a novel marker in the workup of chronic kidney disease, tumour-induced osteomalacia, and rare genetic causes of rickets.

HR is treated with oral phosphorus and calcitriol. Serum levels of calcidiol should be determined in order to exclude a severe vitamin D deficiency. The main aims of the treatment are to improve growth velocity and avoid or reduce skeletal abnormalities<sup>21</sup>. All patients must be carefully monitored after treatment initiation. Radiographic changes may appear

within a week, and physical examination findings may normalise within six months.

The earliest biochemical change after treatment initiation is a rise in the level of phosphorus within the first week<sup>2</sup>. Alkaline phosphatase levels will decrease along the years, achieving normal or just above normal range values<sup>2,22</sup>.

Adjustments to medications are made to accommodate abnormal fluctuations in serum or urine values: elevated alkaline phosphatase and decreased serum phosphorus require an increase in phosphorus dose<sup>21</sup>; increased parathyroid hormone requires an increase in calcitriol and decrease in phosphorus. Calcium to creatinine ratio in spot urine should be determined to detect hypercalciuria<sup>2</sup>, which require a decrease in calcitriol dose.

Lack of compliance, usually associated with phosphorus multiple administrations, is a common problem in this disease (reported in 8/11 children in our study)<sup>23</sup>. Along with late diagnosis, this is responsible for the long-term skeletal abnormalities and short stature observed in these patients (all children with bone deformities; 5/7 submitted to at least one surgery and 5/7 children with final stature below the 3<sup>rd</sup> centile).

Other complications of rickets are nephrocalcinosis (only one child in our study) which justifies performing a renal ultrasonography at 2-5 year intervals. Nephrocalcinosis may occur independently of hypercalcaemia or hypercalciuria, but related to treatment dosages. Another complication is hyperparathyroidism which may progress to tertiary hyperparathyroidism<sup>24</sup>.

Growth hormone has been used as adjunctive therapy in HR, but the results are variable<sup>25-27</sup>. Increases in serum phosphate and linear growth have been reported, as well as worsening leg deformities, radiographic rickets and no effects on final adult height. There is a lack of clear evidence of benefits of this expensive therapy. It is not approved for this disease in our country.

New therapies are also been investigated. In mouse models, anti-FGF23 completely reversed the hypophosphataemia and associated bone disease. Phase 1 and phase 2 trials of humanised monoclonal anti-FGF23 therapy ('KRN23') in humans with X-linked



hypophosphataemic rickets are currently underway (A Repeated Study of KRN23 in Adults With X-Linked Hypophosphataemia; principal investigator: Thomas O Carpenter MD, Yale University; KRN23 is an antibody or a mixture of antibodies against FGF23).

In conclusion, HR is a rare disease with significant long-term morbidities. It should be suspected in children presenting with failure to thrive, developmental delay and orthopaedic abnormalities. Family history should record any hereditary disease. Infants of affected parents must be screened regularly for hypophosphataemia and increased levels of serum alkaline phosphatase to ensure early treatment and avoid morbidities. Treatment requires monitoring and dose adjustment to prevent complications.

**Conflict of interest statement.** None declared.

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