X-linked hypophosphatemic rickets (PHEX mutation): A case report and literature review

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ABSTRACT

Hypophosphatemic rickets is a rare form of rickets that affect children. The diagnosis requires high index of suspicion. We report a case of Hypophosphatemic rickets in 18-month-old Saudi boy presented with delayed walking and lower limb deformity. The diagnosis was confirmed by bone profile, radiological study and genetic testing, which reveled PHEX mutation. The patient was successfully treated by phosphate supplement.

Keywords:

Hypophosphatemic rickets; PHEX gene mutation.

INTRODUCTION

X-linked Hypophosphatemic rickets (XLHR) is a rare form of rickets that affect children. High index of suspicion is needed to diagnose this entity. We report a case of Hypophosphatemic rickets in 18-month-old Saudi boy presented with delayed walking and lower limb deformity.

CASE REPORT

A 18 month old male toddler presented with delayed walking and lower limb deformity. Patient was referred to endocrine outpatient clinic due to persistence of rachitic finding on x ray. Parents consulted primary health care doctor 13 month of age due to delayed walking in comparison to other sibling and observed lower limb deformity (Figure 1). A diagnosis of nutritional rickets was made and started oral cholicalciferol (vitamin D3) 4000 IU once daily. During follow up no noticed improvement in spite of good compliance. There was no history of convulsion, renal or hepatic disease, or similar condition in the family. He was a product of term pregnancy and delivered by normal spontaneous vaginal delivery. There was no consanguinity between parents.

Vaccination was up to date. Developmental parameters were appropriate for age as regard to social, vision, speech and hearing but delayed in gross motor. He just started to walk at 18 month of age (after starting cholicalciferol). He was on formula milk and family diet with average appetite.

On examination not dysmorphic, weight, height, and head circumference were at 25, 10 and 25 percentile respectively. Anterior fontanel was closed and there was frontal bossing. Examination of chest showed bilateral Harrison's salcui and rachitic rosary. There was no hepatosplenomegaly, no skin changes. Child had normal muscle tone and power. The child could walk but had waddling type of get. Musculoskeletal examination revealed widening of the wrist joints and there was significant bowing of the legs (Figure 1). Investigations showed: Hemoglobin 12.3 g dl, white blood cell (WBC) 10.9 × 10^3/μL, neutrophil 21% and lymphocyte 57%.

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Serum urea and electrolytes were normal. Liver function tests were normal. Bone profile; serum Ca 2.4 (normal 2.1–2.5) mmol/L, serum phosphorus 0.6 (normal 0.8–1.5) mmol/L, Serum alkaline phosphatase 1050 (normal 50–136) Unit/LMg 0.8 (normal 0.7–1.03) mmol/L. Serum Parathyroid hormone level 6.4 (normal 1.59–6.89) pmol/L, serum 25 OH vitamin D 214 nmol/L (normal 50–250) and serum 1,25 (OH)2 vitamin D 68 (normal 38–133) pmol/L. Arterial blood gas was normal, and there was normal anion gap. Celiac disease profile was negative. Tubular reabsorption of phosphate was 0.65. X ray knee and wrist showed cupping and fraying of the metaphysis (Figure 2). Gene analysis showed PHEX (**P**hosphate regulating gene with **H**omology to **E**ndopeptidases located on the **X** chromosome) gene mutation, which confirmed the diagnosis of XLR.

Patient was treated with one alphacholicalciferol and oral phosphorus. He was routinely followed up in outpatient clinic. His repeated bone profile parameters improved but he still had significant bowing of the legs at the age of 3 years (Figure 3). An orthopedic consultation was arranged for possible surgical correction.

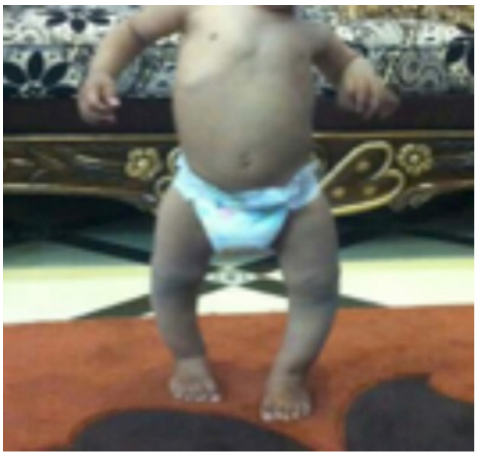

Figure 1 - Bilateral bowing of lower limbs at presentation.

Figure 3 - Patient at age of 3 years of and 6 month showing severe bowing of both legs.

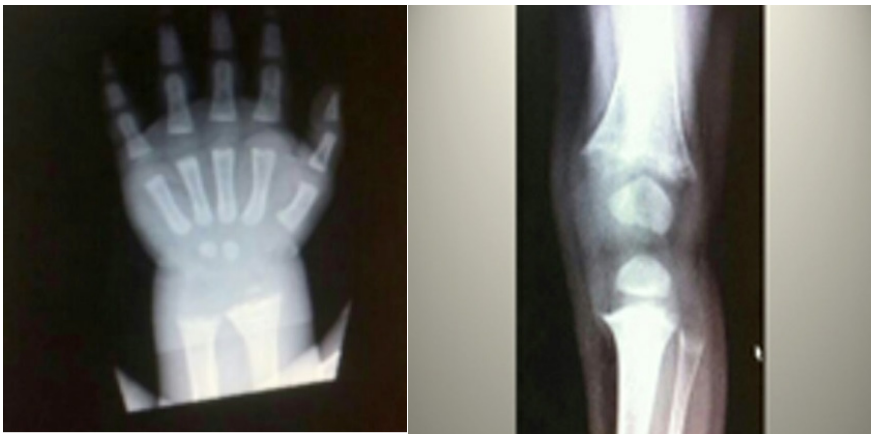

Figure 2 - Rachitic changes in left hand, wrist and left knee.

DISCUSSION

Familial hypophosphatemic rickets is mostly due to renal wasting of phosphate. X-linked hypophosphatemic rickets (XLHR) is the commonest among the other inherited hypophosphatamic Rickets. Estimated incidence is 1:20,000 caused by the mutation in the phosphate regulating gene **P**hosphate regulating gene with **H**omology to **E**ndopeptidases (PHEX) located on the **X** chromosome [1,2]. It is inherited as X-linked dominant. The classical physiologic defect in XLHR is impaired proximal renal tubular reabsorption of phosphate [3].

Phosphorus plays a vital role in growth and development, bone formation, acid-base regulation, and cellular metabolism. Phosphorus exists as organic and inorganic phosphate in the human body. Most of the body's phosphate (85%) remains in the bone associated with calcium as calcium phosphate and it provides structural strength of the bone. Fourteen percent of the total body phosphate is in the cellular level as components of lipids, proteins, nucleic acids and metabolic and signaling pathways [4]. Only 1% of the total body phosphate is in the serum and extracellular fluid [4]. When phosphate is needed for homeostasis, it is fulfilled by bone desorption. Optimal amount of calcium-phosphate ion product is necessary for normal bone mineralization. In young infant and children higher concentrations of phosphate are necessary for adequate skeletal mineralization, and hypophosphatemia and even levels equals to adult normal range are insufficient resulting in rickets.

Serum phosphate concentration usually correlates with the total body phosphate and it is largely determined by the renal tubular reabsorption of phosphate. Filtered phosphate in the urine are mostly (90%) are reabsorbed in the proximal tubule and it is mediated by sodium dependent phosphate co-transporters (NPT2a and NPT2c) [4]. The expression of these co-transporters may be modified by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) [4].

XLHR is caused by mutations in the Phosphate-regulating gene with Homologies to Endopeptidases on the X chromosome (*PHEX*; MIM no. 300550) [2]. Inactivating mutations in *PHEX* result in increase synthesis and secretion of FGF23 [5]. The increased circulating concentrations of FGF23 is responsible for the biochemical phenotype of XLH like phosphaturia, hypophosphatemia and inappropriately low or normal 1,25(OH)2D concentrations [1,16]. FGF23 is a protein synthesized by osteoblasts and osteocytes which inhibits phosphate reabsorption by the renal tubule and if secreted in excess leads to hyperphosphaturia and subsequent hypophosphatemia. Serum concentrations of FGF23 are usually high in patients with XLHR [6].

XLHR is often misdiagnosed as nutritional rickets in young infant like our patient, who was treated for nutritional rickets by oral supplementation of VitaminD3 [7]. Clinical presentation in children with XLHR consists of short stature, genu varum or valgum, flaring of the metaphysis, rachitic rosary and frontal bossing. There is increased frequency of dental decay or periradicular abscesses and bone, muscle, and joint aching and stiffness. Bowing of the leg became more obvious when children starts walking like our patient who presented as significant bowing of the legs and short stature. Clinical manifestations vary in severity from asymptomatic to severe bowing of the legs. Our patient was brought to the primary health care because of delayed walking and there was significant bowing of the legs at 18 month of age.

Identifying important family histories and screening in infancy leads to early recognition of XLHR, even before rachitic deformities are evident. Biochemical features include hypophosphatemia, reduced TmP/GFR, and suppressed 1,25(OH)2D concentrations serum calcium is normal, but secondary hyperparathyroidism is common, both before and after treatment with phosphate [9,10].

Diagnostic evaluation should include fasting serum and urine phosphate and creatinine to confirmation of hypophosphatemia, to determine the tubular threshold maximum for phosphate (TMP/GFR). 25-hydroxyvitamin D should be done to exclude vitamin D deficiency, while 1,25(OH)2D in XLHR is inappropriately low or normal. PTH is frequently mildly elevated at diagnosis but it was normal in our patient.

The classical laboratory finding in XLHR include Hypophosphatemia, normal Serum calcium and

low to normal circulating 1,25(OH)2D levels, normal circulating 25-OHDand high serum alkaline phosphatase[7] as in our patent.

The diagnosis of XLHR is made by characteristic findings of low serum phosphate concentration with a reduced tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR), based on normal values for age. It is confirmed by identification of the *PHEX* gene mutation, though in most reports, mutational detection rates in XLHR patients are approximately 65% [8].

Plasma FGF23 concentration is elevated in XLHR but currently serum FGF23 levels are not measured for the diagnostic evaluation of hypophosphatemic rickets [11,12].

The goals of medical management are the improvement of osteomalacia, rachitic deformities and maximizing growth in affected children rather than to normalize the serum phosphate concentration. Early diagnosis and treatment, beginning prior to walking and the development, leg deformities may be beneficial. Studies have demonstrated better height standard deviation scores (SDS) when calcitriol and phosphate treatment began prior to one year of age [13,14]. However a variable response to treatment has been noted, with many children fail to normalize the growth remains the limitations of the therapy [13,14].

Current treatment of XLHR includes both activated vitamin D (calcitriol or alfacalcidol) and phosphate to correct these deficiencies [7]. Higher doses of calcitriol and phosphate are required to treat XHLR and a recommend doses are phosphate of 20–40 mg/kg/day and calcitriol of 20–30 ng/kg/day keeping in mind that some children require more higher doses [7]. It should be remember that overtreatment with phosphorus and resultant secondary hyperparathyroidism may be harmful for the patient. Goal of treatment efficacy should include height, improvement of skeletal deformity, and radiographic evidence for epiphyseal healing and acceptable height velocity and t in skeletal deformities generally indicate satisfactory dosing. We started both one alpha cholicalciferol and phosphate in therapeutic doses and patient was routinely followed up 3 monthly in outpatient clinic for monitoring his growth parameters, serum, calcium, serum phosphate, alkaline phosphate and serum creatinine.

Biochemical monitoring should be performed in 3 monthly intervals to avoid complications like hypercalcemia, hypercalciuria or hyperparathyroidism [7]. The best biomarker for bone healing is serum alkaline phosphatase activity, which should decreases with treatment suggest optimal bone healing [7]. PTH levels should be measured routinely to identify secondary hyperparathyroidism, which can be corrected by increasing the calcitriol dose, or by reducing the dose of phosphate [7].

Radiological evaluation should be done to exclude the physiological bowing and bone dysplasia. After treatment, radiological evaluation should be repeated for the assessment of healing of rickets, for evaluating skeletal deformities and when considering surgical management. Nephrocalcinosis is a complication of treatment, which is related to the dose of medication, used. Renal ultrasonography is suggested 2-5 year intervals after starting the treatment to detect nephrocalcinosis [15]. We have evaluated our patient by ultrasound and no nephrocalcinosis was detected.

Growth hormone has been tried as an adjunct therapy in XLHR and shown to have an improvement in linear growth and a transient increase in serum phosphate and a transient decrease in urinary phosphate excretion when treated with rhGH [17,18,19]. Increased serum alkaline phosphatase activity, worsening leg deformities and worsening body disproportion have been reported after growth hormone therapy [20]. We did not try growth hormone in our patient.

Surgery during childhood should be avoided. Surgical intervention should be considered if severe bowing or tibial torsion is not improving with medical management. Corrective osteotomies are not usually performed in children under 6 years of age, since medical therapy often improves bow deformities in this age group. Osteotomies are usually deferred until growth has nearly ceased, but severe deformities may require earlier therapy. Orthopedic surgeon should be member of the team managing XLHR patient. We refer the patient to orthopedic surgeon for the opinion because by 3 years of age child had significant lower legs deformities and the patient was booked for corrective osteotomy.

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