X-Linked Hypophosphatemic Rickets: report of a Family from Southern Punjab, Pakistan

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Introduction

Primary hypophosphatemic rickets refer to a larger group of renal phosphate wasting disorders.1 Isolated renal phosphate wasting may result from a number of genetic disorders including X-linked hypophosphatemic rickets (XLH), hereditary hypophosphatemic rickets with hypercalciuria (HHRH), hypophosphatemic bone disease and autosomal dominant hypophosphatemic rickets/ osteomalacia (ADHR). 2

The most commonly identified cause in this group is XLH, that is transmitted in X-linked dominant fashion, but other patterns of inheritance, sporadic and recessive have also been described.3 The incidence estimates are variable, and 1:20,000 population seems to be the most widely quoted figure.4 Acquired forms of primary hypophosphatemic rickets have been described in African children with most between 4 and 7 year of age. 1

XLH is characterized by the defective proximal renal tubular phosphate transport and impaired renal production of 1, 25-dihydroxy vitamin D 3 [1,25-(OH)2 D3].5 The characteristic biochemical abnormalities include hypophosphatemia, due to renal phosphate wasting, normal to slightly low serum calcium, an elevated serum alkaline phosphatase, and normal to slightly high levels of immune reactive parathormone levels6, without an evidence of secondary hyper-parathyroidism.7 The urinary phosphate excretion is large, despite hypophosphatemia and is evidenced by low tubular reabsorption of phosphate (TRP) (Normal: 85-100%) and low threshold tubular maximum reabsorption for phosphate, as expressed per glomeruler filtration rate (TMP/GFR).1 A low TMP/GFR in the setting of a low serum phosphate value documents the inappropriate renal phosphate losses characteristic of primary hypophosphatemic rickets.1,8 Frequent manifestations of XLH in childhood are short stature and femoral or tibial bowing. The short stature, rickets, hypophosphatemia and hyperphosphaturia (as expressed by the low TMP/ GFR) are characteristics of the primary hypophosphatemic rickets and usually have an X-linked mode of inheritance.7 The condition is caused by mutation in the PHEX gene, which is located on Xp 22.1 and encodes a membrane bound endopeptidase. The pathogenic mechanisms by which these mutations result in XLH are not completely understood.5 In this report we describe a family with hypophosphatemic rickets where we believe, the mode of transmission is X-linked dominant. To our knowledge this is the first case being reported from Pakistan.

Case Report

6-year-old child was brought for progressive inability to stand and walk for the last 6 months. He was 4th in birth order among six children of the consanguiant parents and was born at full term as simple vaginal delivery at home. There was nothing suggestive of any other chronic systemic illness. Examination revealed a cooperative, pale child with height 89 centimeter (cm) and weight 12 kilogram (kg) (both less than 3rd centile for his age). He had marked knock-knee and widened legs, to the extent that he could not stand or walk. The inter-maleolar distance was more than 20 cm, in supine position. He had frontal bossing, caput quadratum, widening of the ankle joints, and smooth bowing of the lower legs. The systemic examination was insignificant but the family history was significant (Picture Figure 1).

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Of his five siblings, the sister (C) and three brothers (B, E, F) were normal looking while the eldest brother (A) had mild bowing of the legs and short stature. The mother (G) and paternal grand-mother (K) were reported to have short stature but not the bony deformities.

Other affected Cases

Eldest son

(A): Although he had a chronological age of 14 years, there had also been a failure of linear growth since his childhood, and he had gradually developed mild deformities of the lower limbs. Examination revealed a height of 134 cm and weight of 29 kg (both less than 3rd centile for his age). He had pallor, knock knees, mild anterior bowing of lower limbs and widened ankle joints (Figure 2). The systemic examination was unremarkable.

Father (H):

Now 35 years, had normal weight (91 kg) and height (172 cm) for his age. There was no bony deformity or abnormality on systemic examination. He had been operated at 27 years age for stones in the left kidney. Since then, he has had, off and on, colicky abdominal pain in the left loin.

Paternal Grand Mother (K)

Died at 78 years and was reported to have short stature but no bony deformity. She had been operated for the renal stone at 60 years of age.

The complete blood counts showed mild degree of anemia in the affected subjects (A and D). The serum and urinary calcium were normal in all subjects. None of them had glycosuria or proteinuria except the two affected brothers (A, D) who showed insignificant proteinuria of 1+(<30mg/dl). The alkaline phosphatase was raised in the affected brothers (A and D) and both also had hypophosphatemia. The unaffected subjects were normo-calcemic and normo-phosphatemic. The tubular maximum reabsorption of phosphate per 100 ml glomerular filtration

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rate (TMR/ GFR) was calculated, by using the nomogram of Bijvoet and Walton7 and it was low for the index case (D) i.e. 1.3mg/dl. (Normal: 3.7-5.6) and the affected brother (1.4 mg/dl), proving thereby the case of primary hypophosphatemic rickets.

The tubular reabsorption of phosphate (TRP) was 67.25% and 57.65% (N: 85-100%) in the index case (D) and affected brother (A), respectively. The plasma parathormone levels were normal in both the affected children but 25-hydroxy vitamin D was raised only in the index case (>1000 ng/ml) (N: 9-37.6). Both affected children (A, D) showed sub-clinical hyperthyroidism, while thyroid profile was normal in others (Table). The

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radiological screening revealed advanced changes of rickets in the affected subjects only (Figures 3 and 4). The abdominal ultra sound, surprisingly, revealed hypoplastic right kidney in the index case. Abdominal ultra sonographic screening of other family members showed nephro-calcinosis and chronic damage in the kidney of all siblings except the sister and the youngest brother (F) of 2 years age. The father had right hypoplastic kidney and mother had left hypoplastic kidney. The serum urea, creatinine and complete urine examination was normal in these subjects.

Discussion

In our region, the most common cause of rickets is malnutrition, although other causes of rickets are now also being recognized.7 In this reported family the female child is spared while the male children are affected. Historically, the paternal aunty (the father's sister) is spared while paternal grandmother was affected. This suggests that the transmission of the disease is X-linked.

The vitamin D deficiency rickets has almost been eradicated in the developed world and as a cause of rickets, the vitamin D deficiency was not considered by 1940s. Familial (X-linked) hypophosphatemia is the most common cause of inherited rickets in the North America.9 The Albright and co-workers first described this entity in 1937.10 The phenotypic trait of hypophosphatemia is transmitted on the X-chromosome. The patients with familial hypophosphatemic rickets are picked up by severe rickets with normocalcemia, hypophosphatemia and hyperphosphaturia.3 The phosphaturia despite hypophosphatemia indicates a defect in the renal tubular reabsorption of phosphate. This phosphaturia is unassociated with aminoaciduria, glucosuria, bicorbonateuria or kaliuria.3 The alkaline phosphatase activity is elevated but usually is less than the 10-15 fold elevation often seen in patients with vitamin D deficiency or in the hereditary resistance to vitamin D.1 The parathormone level in the serum are either normal or mildly increased.7 The serum levels of 25-hydroxy vitamin D are normal but may be increased in some cases.7 Children affected with this disorder develop lower limb deformities. The deformities progressively worsen in an otherwise well-nourished and healthy child. The rate of linear growth is at first normal and then slowed, ultimately resulting in short

stature.7 The tetany, myopathy, rachitic rosary, harrison sulcus are usually absent.4 Pulp deformities and dental abscesses may be encountered. 1

The restriction fragment polymorphisms studies in several kindered of X-linked hypophosphatemia have found the mutant gene mapped on the short arm of the chromosomes (Xp22.1). X-linked hypophosphatemia is caused by inactivating mutations in a phosphate regulating endopeptidase called PHEX (previously called Pex).5 It exhibits homology to a family of the endopeptidase genes and several mutations, including deletions, frame shifts and splice-junction defects have been reported. 1

The pathogenesis of nephrocalcinosis in children with XLH is probably multifactorial.11 It is suggested that the cause is intratubular deposition of calcium phosphate, due to the super saturation of the urine with the calcium that results in intratubular crystal formation at the tip of the renal papilla.11 The increased urinary calcium excretion is a common complication of vitamin D and oral phosphate therapy. 12

The treatment of such children is a therapeutic challenge .The administration of 1-25 dihydroxyvitamin D and phosphate significantly improves the clinical course of the disease in the childhood.7 As for the likely mechanism, Azam et al have shown in mouse model that feeding a high phosphate diet is without any effect in wild type mice, whereas in XLH mice(hyp) the same diet induced 3-fold and 2-fold increases, respectively, in renal enzyme (1-alpha hydroxylase) activity and messenger ribonucleotide abundance (m RNA). 13

The other children of the family should be screened with the serum and the urinary phosphate level and serum alkaline phosphatase activity. These tests may be performedevery three-months starting from the first month of life. Any result suggestive of XLH warrants radiological follow-up and if positive, treatment should be started.1 It has been shown quite conclusively that early treatment before 1 year of age resulted in improved height outcome at all stages of growth, with somewhat milder X-ray changes in disease activity and improved biochemistry, and without an increased rate of treatment related complication.5 Fibroblast growth factor 23 (FGF-23) has shown a role in the homeostasis of phosphate and it's measurement may indicate the activity of the disease.14 So this can be used as a diagnostic and prognostic tool in these patients.

References

1. 1. Carpenter TO. New perspectives on the biology and treatment of x-linked hypophosphatemic rickets; pediatric endocrinology. Pediatr Clin North Am 1997;44:443-66.
2. Nehgme R, John T, Smith C, et al. Cardiovascular abnormalities in patients with x-linked hypophosphatemia. J Clin Endocrinol Metab 1997;82:2450- 4.
3. Chesney RW. Metabolic bone disease. Iin: Nelson WE. ed. Textbook of pediatrics. 16th ed. Philadelphia: WB Saunders,2001 pp. 2132-8.
4. Rasmussen H, Tenehouse HS. Mendelian hypophosphatemia. In: Seriver CR, Beandet AL, Sly WS, et al. ed. The molecular and metabolic basis of inherited diseases, 7th ed. New York: McGraw - Hill, 1994, p. 3717.
5. Makitie O, Doria A, Kooh SW, et al. Early treatment improves growth and biochemical and Radiographic outcome in x-linked hypophosphatemic rickets. J Clin Endocrinol Metab 2003;88:3591-7.
6. Sullivan W, Carpenter T, Glorieus F, et al. A prospective trial of phosphate and 1-25 dihydroxy vitamin D3 therapy in symptomatic adults with x-linked hypophosphatemic rickets. J Clin Endocrinol Metab 1992;75:879-85.
7. Zargar AH, Laway BA, Masordi SR, et al. Hereditary hypophosphatemic rickets; report of a family from the Indian subcontinent. Postgrad Med J 1999; 75:485-7.
8. Walton RJ, Bijvoet OI. Nomogram for derivation of renal threshold phosphate concentration. Lancet 1975;2:309-10.
9. Rasmussen H, Tenenhouse HS. Hypophosphatemia. In: Seriver CR, Beandet AL, Sly WS, et al. eds. The metabolic basis of inherited diseases. New York: McGraw-Hill, 1989, pp. 2581-604.
10. Albright F, Butler AM, Bloomberg E. Rickets resistant to vitamin D therapy. J Clin Dis child 1937;54:529-47.
11. Movin G, Seikaly MG, Baum M. Thiazide diuretics arrest the progression of nephrocalcinosis in children with x-linked hypophosphatemia. Pediatrics 2001;108:6.
12. Verge CF, Lam A, Simpson JM, et al.

Effects of therapy in x-linked hypophosphatemic rickets. N Eng J Med 1991;325:1843-8.
13. Azam N, Martin ZYH, Wang X, et al. Disordered regulation of renal 25 -hydroxyvitamin D-1 a-hydroxylase gene expression by phosphorus in x-linked hypophosphatemic (Hyp) mice. Endocrinology2003;144:3463-8.
14. Jonsson KB, Zahradnik R, Larsson T, et. al. Fibroblast growth factor-23 in oncogenic osteomalacia and x-linked hypophosphatemia. N Engl J Med 2003; 348:1656-63.