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Familial Hypophosphatemic Rickets - A Case Report and Review of Literature

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Introduction

Familial hypophosphatemic or X-linked hypophosphatemic (XLH) rickets is the most common form of non-nutritional rickets[1]. The prevalence of XLH rickets yet remain unknown in Bangladesh. It is an X-linked dominant disorder characterized by renal phosphate wasting with consequent defect of bone mineralization[1]. Some form of the disease are observed to be transmitted which followed an autosomal dominant fashion and few sporadic cases are also being reported[2]. The basic problem in this disorder is a defect in renal phosphate transport across the luminal membrane of proximal renal tubular cells causing phosphate wasting with consequent hypophosphatemia. Affected children usually have short stature, knock knee, bowing of legs, coxa vara and poor dental development, but Harrison's sulcus, myopathy are uncommon[3]. The human phosphate-regulating gene is responsible for X-linked hypophosphatemic (XLH) rickets.

Case Report

A 11 years old girl of a consanguineous parents belonging to a low socioeconomic status, hailing from Nazirabazar, Dhaka, was admitted at Dhaka Medical College Hospital on 07/03/07 with inward bending of both legs for last 4 years, not gaining height in comparison to other children of same age and dental caries for 2-3 years. She had no history of polyuria, dysuria, jaundice, recurrent chest infections or recurrent attacks of diarrhoea and not on long term anticonvulsant drugs. Birth history was uneventful and was partially immunized as per EPI schedule. After birth she was predominantly breast fed for only 5 successive months and currently she is on family diet, i.e., rice, vegetable, fruits but low quantity of fish, meat, milk and egg as they are unable to afford those. Though her milestones of development were normal, her linear growth and also weight were not satisfactory as compared to that of other children of her age. Exposure to sunlight was adequate as she used to play along with other children in open air. Her father did not have the same disease and died of kidney disease two years back. Her mother and sibs are healthy.

On examination, her pulse was 40/min, BP-100/60 mm Hg and temperature was normal. Anthropometric measurement revealed height - 108 cm (74.2% of NCHS median), weight - 18 kg (55.3% of NCHS median) and weight for height - 98.5% of NCHS median. Both wrist and knee joints were widened (Fig.-1), knocked knee (Fig.-2) was obvious on standing. The chest examination demonstrated pegion chest deformity, mild rachitic rosary but there was no Harrison's sulcus or other deformities of the limbs or joints. However, dental caries were present in both upper and lower molar teeth.

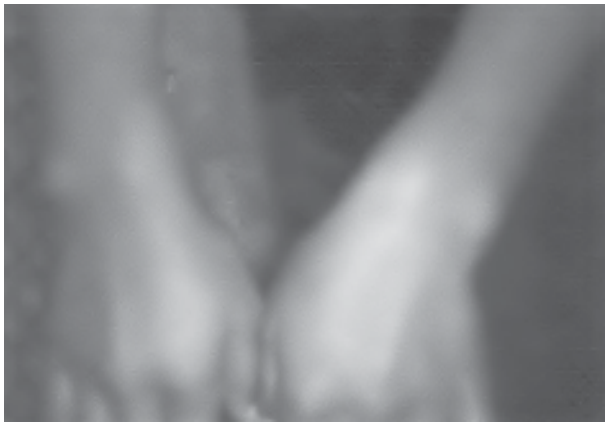

Fig.-1: *Widen wrist joints*

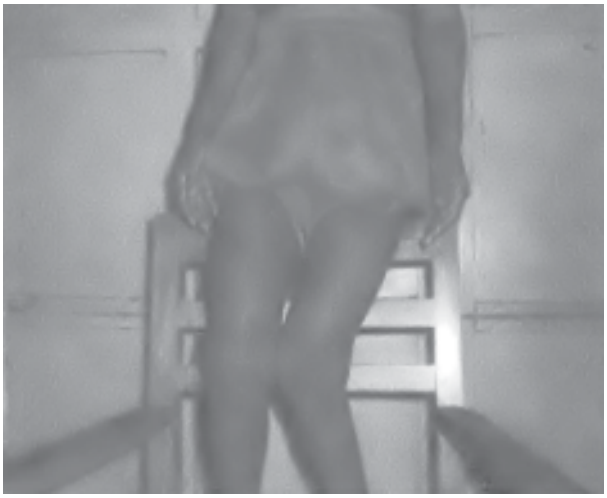

Fig.-2: *Knock Knee*

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Radiologically, cupping, fraying and widening (Fig.-3) of growing lower ends of femur as well as radius and ulna, thinning of cortex and generalized osteopenia were revealed.

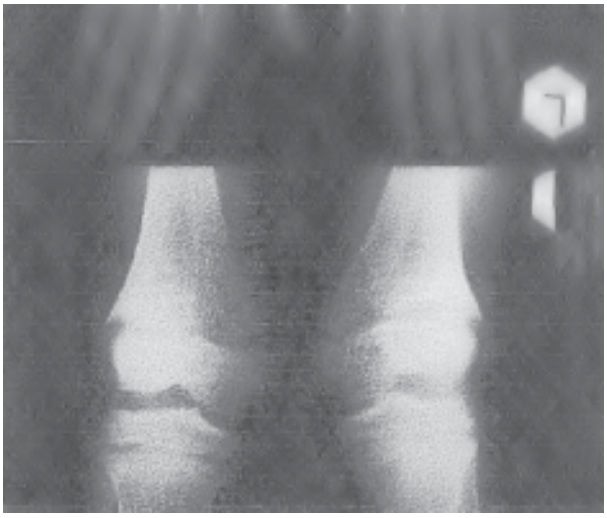

Fig.-3: *X-ray knee joints showing radiological changes of rickets*

Laboratory investigations showed TC of WBC 8000/cmm, DC: polymorph 60%, lymphocyte 37%, monocyte 2%, basophil 1%, eosinophil 2%. Total platelet count was within normal range. Anisocytosis and poikilocytosis of RBC and mature WBC were showed in peripheral blood film. Biochemical investigations showed near normal serum calcium (Ca^{++}) level of 8.4 mg/dL (N: 8.8-10.8 mg/dL), serum phosphate 2.5 mg/dL (N: 4-7 mg/dL), while alkaline phosphatase was 630 IU/L which was much higher than normal range (N: 115-431 IU/L). Serum creatinine was 0.8 mg/dL and SGPT 40 IU/dL. The parathyroid hormone level was within normal limit 11 pg/mL (N: 7-53 pg/mL). Urine examination showed phosphaturia and its level was 24.5 mg/dL. Urinary creatinine was 22.5 mg/dL (N: 15-20mg/dL). As there is no definite range of the urinary phosphate level of 11 years old girl, tubular reabsorption of phosphorus (TRP) was calculated by using the following equation, expressed as percentage[4].

TRP = 100[1- (Scr X Upo_4) / (Spo_4 X Ucr)], where Scr = serum creatinine, Spo_4 = serum phosphate, Ucr = urinary creatinine, Upo_4= urinary phosphate. All values are in mg/dL. TRP depends on serum phosphate (Spo_4)[4]. The TRP was 68% (N: 78-98%) which confirmed loss of excess phosphate through urine. However, serum 1-α-hydroxylase level could not be done. All parameters of electrolytes were normal. Benedict's test showed no glucosuria.

Both the clinical features and laboratory parameters were consistent with familial hypophosphatemic rickets. So, she was treated with Joulie solution, an oral phosphate suspension made up of sodium phosphate (136 gm/L) and phosphoric acid (58.8 gm/L)[5] 1.5 tsf every 4 hourly. Active form of vitamine D (1-25 dihydroxy cholecalciferol) was also given in the form of Dicatrol capsule (0.25mcg) 6 hourly.

Along with treatment we consulted with orthopaedic department. She was advised to continue the treatment and for regular follow up. After 2 weeks of treatment with oral phosphate and dicatrol, significant radiological improvement was documented. Genetic counseling was also done. As the disease is X-linked, the defective gene may come either from father or from mother. Unfortunately, the genetic study is not possible in Bangladesh. As the father died two years back, there is no chance to have any more children.

Discussion

Familial hypophosphatemic or XLH rickets is one of the most common non-nutritional rickets, though it is less reported among paediatric group[7]. Generally, it is the late onset disease, not common in toddler group, like nutritional rickets[7]. However, it is more common among the growing age when he/she can bear weight. As the disease reported to be familial and X-linked dominant, female children are affected more than their male counterparts. Father (XY) transmits only to daughter and mother (XX) transmit to both son and daughter. So, the over all ratios for girls are more. In this case, as because both father and mother did not suffer from this disease and also because all the siblings are healthy, so, it is presumed that this case may be a sporadic one. The classical features of rickets such as rachitic rosary, Harrison's sulcus, myopathy, etc are less common in this disease rather visible knock-knee, bowing leg, short stature, coxa vara, genu varum / valga and tooth defects are more profound[6]. In this case knock-knee, short stature, pigeon chest, mild form of rachitic rosary and tooth defects were observed.

Serum phosphate was significantly low. The TRP of this child was 68%, which was far less than the normal value (ranging from 78-98%). This indicates that she was losing more phosphorus in urine than her normal counterparts. TRP depends on serum phosphate level and it should be grossly above 80% in normal

individual[4]. This low TRP also reflects the basic pathophysiology of the disease, i.e., impaired renal transport of phosphate across the tubular cells. In nutritional rickets there is low concentration of active form of vitamin D, leading impairment of absorption of both Ca^{++} and Po_4 from intestine. When serum Ca^{++} level falls, it stimulates parathyroid hormone (PTH) secretion, which in turn maintains the normal serum Ca^{++} level by resorption of $Ca^{++}$from bone, rather than conserving from intestine and kidney. So, the Ca^{++} level in blood may remain within limit due to secondary hyperparathyroidism. This PTH also causes phosphates diuresis effect on kidneys lowering the serum phosphate[7]. But in this case, she has phosphaturia, not due to secondary hyperparathyroidism as PTH level was normal, as expected. The mechanism of phosphaturia is quite different in case of XLH. Here the defect lies in the proximal tubule of the kidney, since it fails to conserve the PO_4, resulting in ultimate hypophosphatemia. There is absolutely no role of PTH and there is no secondary parathyroid hormone secretion[6,8].

Standard therapeutic management of this genetic disorder includes oral phosphate supplementation - Joulie solution: 7.5ml 4 hourly, and 0.5 to 2.0 mcg of 1,25-dihydroxy-cholecalciferol: calcitriol (Dicatrol), in divided doses. However, oral phosphate in capsule form providing 250mg of phosphorus per capsule, have been suggested, alternatively. Progressive healing is usually demonstrated on repeated radiological images after 2-4 weeks of treatment. In this case, it was revealed after 2 weeks. As it is a genetic disorder this has to be continued for life long. Routine monitoring of serum Ca^{++} and Po_4 level was also advised which would probably lead her towards good prognosis as reported else where[9,10]. Another case of XLH rickets was reported in 2003 where the presentation was knock knee in a four years old girl[11]. In that case serum Ca^{++} 9.12 mg/dL, serum PO_4 2.2 mg/dL, serum alkaline phosphatase 1242 U/L, serum urea 6 mmol/L, serum creatinine 1mg/dL, serum bilirubin 0.8 mg/dL and TRP 41.2% were found.

Conclusion

In conclusion, it can be stated that XLH must be considered as a differential diagnosis with any form of rickets, who has positive family history, presence of bowing of legs, knock knee, coxa vara, genu varum (rather than Harrison's sulcus, rachitic rosary or myopathy), hypophosphatemia with corresponding phosphaturia and normal serum PTH level. However, renal, hepatic or other related causes should also be excluded as differential diagnosis.

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