Hereditary Hypophosphatemic Rickets presenting to a Tertiary Care Centre in South India

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ABSTRACT

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Hypophosphatemic rickets was first described by Albright et al. in 1937. It may be hereditary or acquired. It is characterized by persistent hypophosphatemia and hyperphosphaturia. Among the inherited hypophosphatemic rickets, the most predominant type is inherited in an X-linked pattern due to the mutation in the gene encoding the phosphate-regulating endopeptidase homolog, Xlinked (PHEX). The other types being autosomal dominant and autosomal recessive. In this report we present 3 cases of hypophosphatemic rickets, presenting with skeletal and dental abnormalitites, their clinical features, radiological findings and genetics are described. Although rare the awareness of such cases is important for pediatricians, orthopaedicians, endocrinologist s and nephrologists alike. Early diagnosis and treatment of hypophosphatemic rickets with a team approach is of utmost importance as it may prevent subsequent sequelae.

Keywords: Hypophosphatemia, Rickets, Hereditary, X Linked, Osteomalacia

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BACKGROUND

Rickets is classified as calcipenic and phosphopenic. Hypophosphatemia is common in both groups of rickets.[1] Hypophosphatemia prevents apoptosis in the hypertrophic cells in the growth plate. In the absence of apoptosis, the hypertrophic cells accumulate in the growth plate and form the rachitic bone. In phosphopenic rickets (hypophosphatemic rickets), phosphate deficiency is the primary defect that results most commonly from increased renal excretion of phosphorus. Hypophosphatemic rickets is the most common type of nonazotemic, refractory rickets in Indian children.[2] Early diagnosis and prompt treatment of hypophosphatemic rickets is of utmost importance to prevent sequelae. This case series describes 3 different presentations and causes of hypophosphatemic rickets.

CASE 1 :

18 year 9 month old female, 3rd child of non-consanguineous marriage presented with bowing of limbs and delayed primary dentition at one and a half years age. She had history of recurrent dental caries and disintegration of teeth but no history of any fractures. There was progressive worsening of the bowing for which

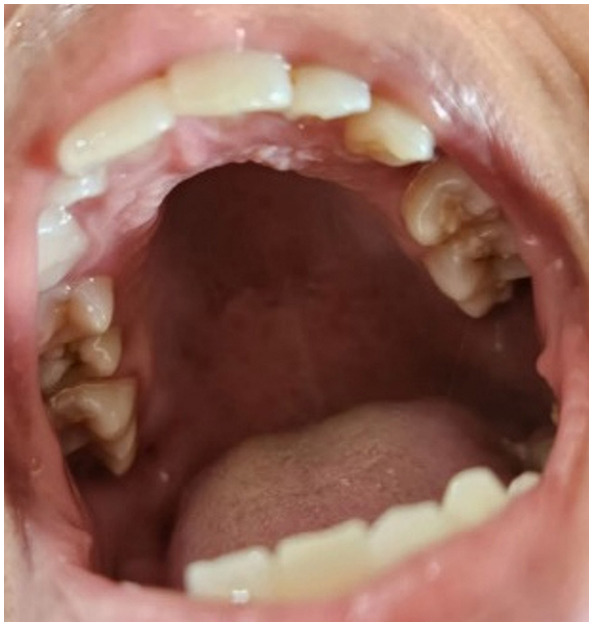

Figure 1. **Dental caries**

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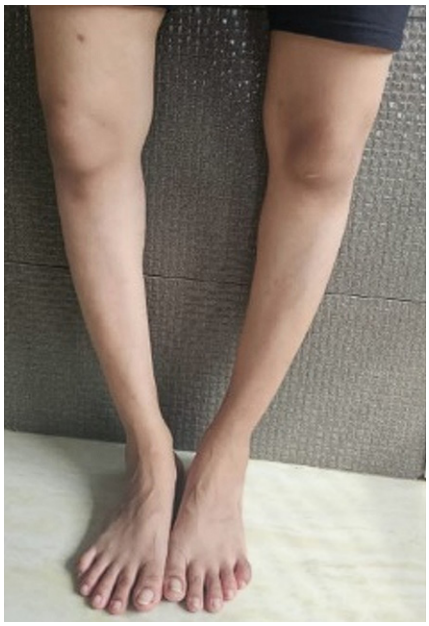

Figure 2. **Genu varum**

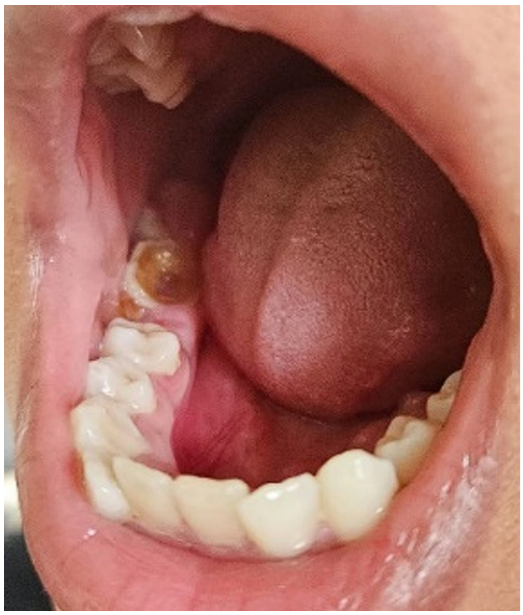

Figure 3. **Dental abscess**

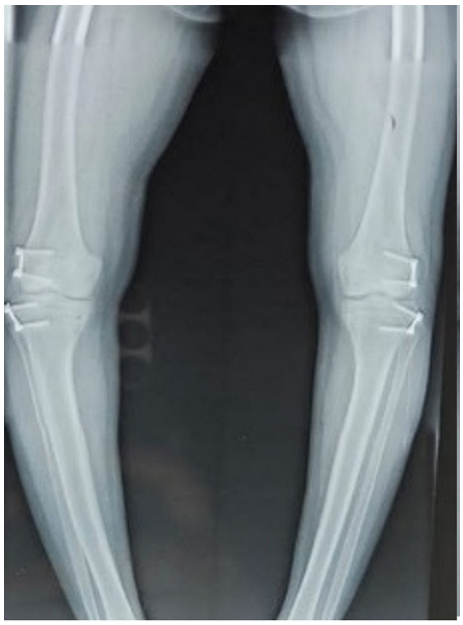

Figure 4. **Knee radiograph showing Epiphyseodesis plate**

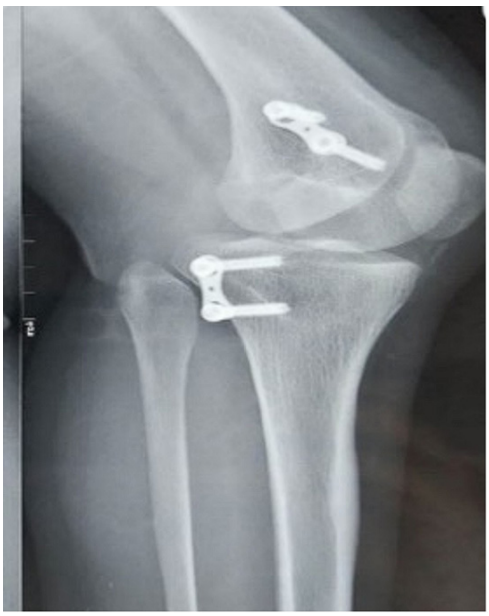

Figure 5. **Knee radiograph showing Epiphyseodesis plate on lateral view**

an epiphysiodesis plate was inserted to stop further bowing, at the age of 14 years. Patient was referred to our department for further assessment.

On examination – Anthropometric measures were as follows- Height 142 cm (<3 rd centile), Weight 40 kg (3-10th centile), BMI-20 kg/m2, Upper Segment (US)-78cm, Lower Segment (LS) 86 cm, US: LS ratio - 0.88, Inter malleolar distance- 2 cm (normal), Intercondylar distance- 12cm (high). There was no evidence of wrist widening, Harrison's sulcus, rachitic rosary or cataract.

INVESTIGATIONS

Her serum calcium was 9.6mg/dl, phosphate was 2.3mg/dl, albumin was 4.1g/dl and ALP 106 IU/L. Urine evaluation with 4 hour timed collection was done, Urine creatinine was 45.77 mg/dl, and Urine phosphorus was 24.4 mg/dl, with which Tubular maximum of Phosphorur adjusted for GFR (Tmp/GFR) was calculated as 1.95. 25 hydroxy Vit D was 41.8ng/ml, Urine pH was 4.25, ABG had no acidosis, Bicarbonate was 24 meq/L.

Genetic analysis was done which showed PHEX gene mutation on exon 22 location, p.Arg747Ter location, mode of inheritance being X linked dominant.

CASE 2 :

18 years, 3 month old male, 2nd child of 3rd degree consanguineous marriage, was asymptomatic till 8 years of age. He presented with inward bowing of both legs, and history of swelling of both knees. It was gradual in onset, progressive in nature. Mother also noticed he was short compared to peers. Short stature was noticed from about 10 years of age onwards.

On examination : Genu valgum and pectus carinatum were present. Intermalleolar distance was 19cm. Anthropometry measurements were as follows- Height 146 cm (<3rd centile -3.3 SDS), Weight 42 kg (3rd centile; -1.9 SDS), BMI – 19.7 kg/m^2, MPH 170 cm (25-50th centile), Head circumference: 54 cm, US: LS ratio – 0.8

Figure 6. **Genu valgum**

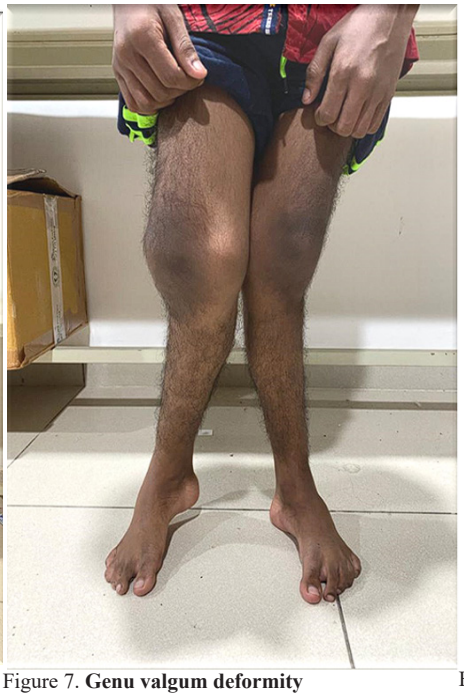

Figure 7. **Genu valgum deformity**

Figure 8. **Pectus carinatum**

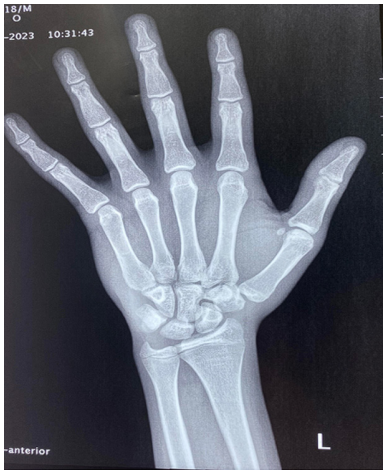

Figure 9. **X ray hand in Dent's disease. No apparent changes are seen as the bone fusion has occurred**

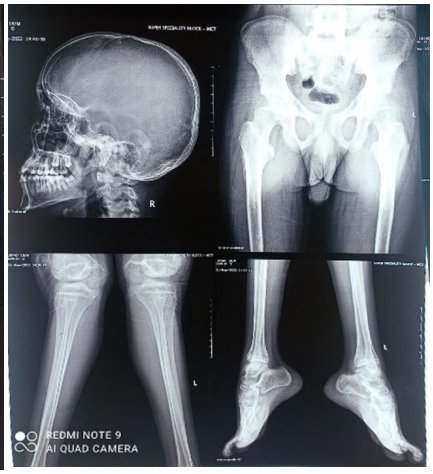

Figure 10. **Skeletal survey in Dent's disease**

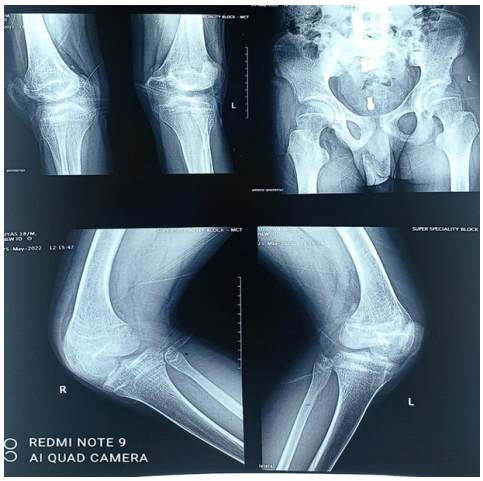

Figure 11. **Skeletal survey in Dent's disease**

INVESTIGATION

S. Potassium was 3.1 mEq/L, S. Phosphorus 1.5 mg/dl, ALP was 429 IU/L, Urine albuminuria present, Urine sugar 2%. Urine pH 5.2. Urine potassium 53.3 mmol, urine creatinine 65 mg/dl, urine phosphorus was 47.09 mg/dl. TMP 62 % . 24 hour urine calcium was 320 mg (7.6 mg/kg/hour) , 24 hour urine creatinine was 923 mg. Urine calcium creatinine ratio was 0.34, 24 hour protein was 850 mg. Genetic analysis was not affordable for the patient.

As this patient presented with bilateral genu valgum, renal phosphate wasting, proximal tubular dysfunction, hypokalaemia, phosphaturia, proteinuria, glycosuria and hypercalciuria, Dent's disease was kept as diagnosis and Urine Beta 2 microglobulin- 4000mcg/L (Normal <150). Dents disease was kept as diagnosis. Urine beta 2 microglobulin sent and was elevated 4000mcg/L. (normal <150 mcg/L).

Patient was started on sodium acid phosphate sachet (elemental P-500mg) 1⁄2 QID and Hydrochlorothiazide 12.5mg. At discharge his serum Phosphorus was 2.9 mg/dl. Patient was then referred to Orthopaedics department for corrective surgery.

CASE 3 :

1 year 4 month old - male child presented with complaints of, widening of wrist and depression in lower chest at 9 months of age. There was no history

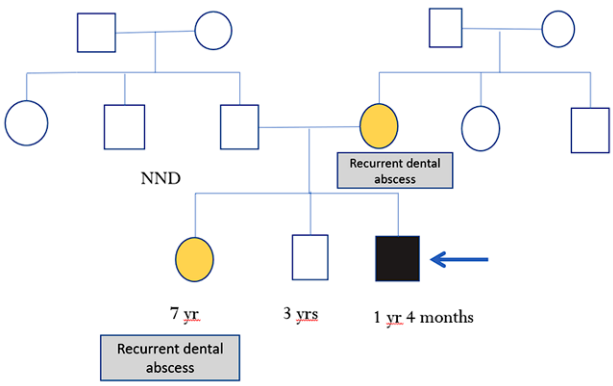

Figure 12. **Pedigree chart showing autosomal dominant inheritance**

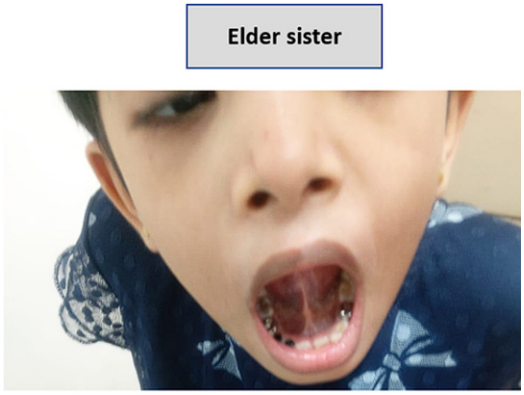

Figure 13. **Dental abscesses**

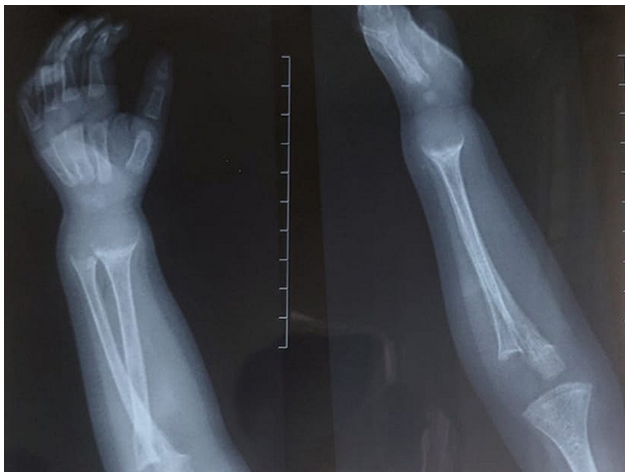

Figure 14. **X rays showing fraying, Cupping and Widening of growth plate in upper limb**

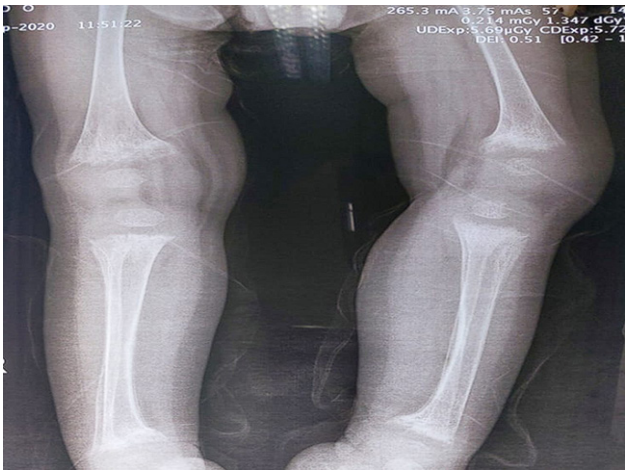

Figure 15. **X rays showing Fraying, Cupping and Widening of growth plate in lower limb**

of bowing of legs or swelling in knees or ankles. Child received 7 lakh units of Vitamin D3 for 4 months for above complaints. However there was progressive worsening of deformities. There was no history of renal disease or malabsorption. First tooth eruption was at 10 months. There was no history of dental abscess or dental caries.

On examination, he was found to have Dolichocephalic head, Anterior fontanelle -2 X 2, posterior fontanelle closed. There was no frontal bossing. Widening of both wrists and pectus excavatum was present. Anthropometric measurements were as follows- weight was 8.5 kg (3rd to 15th centile), length was 70 cm <3rd centile, (-2.8 standard deviation score), Upper segment : lower segment ratio was 1.3, head circumference was 47 cm (50th to 75th centile).

INVESTIGATIONS :

Serum calcium was 9.3 mg/dl, serum phosphorus was 2 mg/dl, ALP was 1443 IU/L. 25 hydroxy vitamin D was 31.6 ng/ml. Serum creatinine was 0.25 mg/dl, urine Ph 5.1, serum bicarbonate was 22 mmol/L. Urine calcium 0.85 mg/dl, urine creatinine 20.4 mg/dl, urine calcium creatinine ratio was 0.04 mg/mg,urine phosphorum was 37.8 mg/dl, TRP was 71%, Tmp-GFR calculated as 1.9 mg/dl.

Genetic Analysis was sent which showed mutation in FGF23 gene, at exon 3 location, p.Arg179Gln, autosomal dominant mode of inheritance of hypophosphatemic rickets.

DISCUSSION :

Hypophosphatemic rickets is among the differential diagnoses of rickets in childhood, and its initial therapy is composed of phosphorus and calcitriol replacement. The improvement in growth can be observed in the first year of therapy, especially in prepubertal children.

The most important differential diagnoses to be considered are Fanconi syndrome and nutritional

rickets. The Fanconi syndrome shows metabolic acidosis, hypouricemia, proteinuria and serum and urinary changes of other electrolytes, besides episodes of recurrent dehydrations. Nutritional rickets shows changes in bone metabolism, however, the rate of the tubular reabsorption of phosphate is close to 100%. These diseases were ruled out as the patients did not present with acid-base disorders or proteinuria. Urinary phosphate loss associated with hypophosphatemia was observed.

Even though the diagnosis and initial treatment of hypophosphatemic rickets can be conducted without molecular diagnosis, the detailed diagnosis obtained by the genetic investigation is important, mainly for genetic counselling.

X-linked hypophosphatemic rickets, described in 1958, is the most common form of primary rickets, with incidence of 1:20,000.[3] It is characterized by a impairment in the proximal tubular reabsorption of phosphate, secondary to the mutation in the "phosphate-regulating gene with homologies for endopeptidases in chromosome X" (PHEX gene). With the mutation in PHEX, the degradation and inactivation of FGF 23 is decreased, resulting in the increased excretion of phosphate and in the compromise of bone mineralization.

Autosomal dominant hypophosphatemic rickets, described in 1971,[3] occurs because of mutations in the gene of FGF23 in chromosome 12p13, with gain in function, resulting in high levels of FGF23 activity. FGF23,besides inhibiting the reabsorption of renal phosphate, also stops the synthesis of calcitriol, active form of vitamin D.[4] In this type of rickets, there is phosphaturia, normal or reduced serum vitamin D3, and skeletal changes that are typical of this pathology, such as fractures, rachitic rosary and/or osteomalacia.

Dent's disease is a group of X-linked recessive syndromes associated with hypercalciuric nephrolithiasis, all presenting with an underlying mutation in CLC-5 chloride transporter encoded by the CLCN5 gene: presenting as X-linked recessive nephrolithiasis, X-linked recessive hypophosphatemic rickets, and LMW proteinuria with hypercalciuria and nephrocalcinosis.[5] This heterogenous group, is an infrequent disorder documented in ~ 250 families worldwide.[6]

The case series shows the presence of non-nutritional rickets resistant to vitamin D treatment in clinical practice in India. It highlights the need for heightened awareness regarding hereditary hypophosphatemic rickets among paediatricians, orthopaedic and endocrinologists.

END NOTE

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Conflict of Interest: None declared

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