INTRODUCTION
Rickets is characterized by softening of bones due to defective mineralization of cartilage in the epiphyseal growth plate leading to widening of ends of the long bones, skeletal deformities in children. Familial Hypophosphatemic rickets is the most commonly inherited, non-nutritional form of refractory rickets. It is being inherited as X-linked dominant with variable penetrance. The underlying defect involves impaired proximal tubular reabsorption of phosphate.

CASE HISTORY
A 15 year old girl, presented with progressive bowing of the legs and difficulty in walking since 5 years of age. She was the second child of non-consanguineous parents, born normally at term. Neonatal and post neonatal period was uneventful. She was on exclusive breast feeds and immunized. No other family members had same complaints. Her dietary history was normal, history of sun exposure and she attained menarche at the appropriate age. No H/O jaundice/clay coloured stools/steatorrhoea/tetany/convulsion/fracture/dental caries. No H/O DM/epilepsy/TB. H/O injection of vitamin D and intake of T.Calcidiol since 5 years of age on and off, oral phosphate 2 g/day since 8 years of age on and off. Now vitamin D discontinued for last 2 months.

ON EXAMINATION
- Short stature
- Frontal bossing
- Wrist widening
- Ricketty rosary
- Harrison sulcus
- Anterior-medial bowing of lower limbs
- Genu valgum
- Kyphosis were observed.
- No alopecia was noted.
Height-138 cm, BP-110/70 mmHg, vitals – normal, other systemic examination- normal.
Biochemical Investigation details:
S. Calcium - 9.5 mg/dl (8.4-10.2)
Phosphate - 2.2 mg/dl (2.5-4.5)
Alkaline phosphatase - 320 IU/L (52-170)
25 hydroxy Vitamin D - 22.5 ng/ml (30-100)
Parathormone - 38.16 pg/ml (15-65)
Tubular reabsorption of phosphate – 70% (84-100%)
Urea - 24 mg/dl (15-40)
Creatinine - 0.8 mg/dl (0.6-1.1)
S.Electrolytes, Thyroid function test, Arterial blood gas analysis – normal
Biochemical parameters are analysed by using following method:
- Calcium is measured by O-cresolphthalin complexone method
- Phosphate by UV phosphomolybdate
- 25 hydroxy vitamin D and parathormone by chemiluminescent immunoassay
- Alkaline phosphatase is measured by kinetic ALP-AMP method
- Electrolytes by ion selective method
- Thyroid function test by chemiluminescent immunoassay
- ABG by blood gas analyser
- Tubular reabsorption of phosphate is calculated by using formula.
TRP = 1 - [(urinephosphate/ plasmaphosphate)/(urinecreatinine/plasmacreatinine)]

Rickets is due to defective mineralization of cartilage in the epiphyseal growth plate leading to widening of ends of the long bones, skeletal deformities in children.

There are different types of rickets. They are:
- Vitamin D deficient rickets (Nutritional)
- Vitamin D dependent rickets type I & II
- Familial Hypophosphatemic rickets
- Renal rickets

**Nutritional rickets (I):**
- Calcium - Normal/Low
- Phosphate - Low
- Alkaline phosphatase - Increased
- Parathormone - Increased
- Vitamin D3 - Decreased

**Vitamin D dependent rickets (I):**
Vitamin D dependent rickets type I is an autosomal recessive disorder due to mutation of gene that encodes 25 hydroxy vitamin D3- 1 alpha hydroxylase. This leads to decreased formation of 1,25 dihydroxy vitamin D3 which is the active form of vitamin D3.

Type II vitamin D dependent rickets is an autosomal recessive disorder due to vitamin D receptor mutation which leads to end-organ resistance to active form of vitamin D3. Alopecia is the characteristic feature. Higher doses of vitamin D improves the manifestation of the disease. X-ray changes occur in 2 to 3 weeks of vitamin D administration along with calcium.

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**Proximal renal tubular acidosis (Fanconi syndrome):**

It is due to impairment of bicarbonate reabsorption in the proximal tubule. Also associated with amino aciduria, glycosuria, phosphaturia.

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**Familial hypophosphatemic rickets:**

The syndrome of rickets resistant to normal therapeutic doses of vitamin D3, but responds to massive doses of vitamin D3 was first described by Albright, Butler and Bloomberg in 1927(2). Symptoms probably begin within the first year of life. First symptom is bowing of the legs, short stature, cranial bossing, beading of the ribs, enlargement of knees, wrists, ankles. It has X-linked, autosomal dominant and autosomal recessive inheritance.

X-linked hypophosphatemic rickets is a dominant disorder and accounts more than 80 % of familial hypophosphatemic rickets. PHEX (Phosphate regulating endopeptidase homolog, X-linked) gene is mutated in X-linked hypophosphatemic rickets (3) and its prevalence is 1 : 20,000 (4). PHEX gene is located in X chromosome p 22.2 and active primarily in bone and teeth. It helps in formation and growth of the bones. PHEX protein is involved in regulating the balance of phosphate in the body. PHEX gene regulates Fibroblast Growth Factor 23 which inhibits phosphate reabsorption by the kidney. If PHEX gene gets mutated it leads to increased production or reduce breakdown of Fibroblast Growth Factor 23, hence causes decreased reabsorption of phosphate by the kidney which leads to hypophosphatemia (5).

In such cases the Investigation: low Phosphate, normal/low S.Calcium, increase Alkaline phosphatase, normal/
low Vitamin D, normal/mild PTH, fractional tubular re-absorption of phosphate is low. Low serum phosphate and reduced tubular reabsorption of phosphate corrected for GFR is the diagnostic feature of X-linked hypophosphatemic rickets (6).

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TRP = 1 - \frac{(urinephosphate/ plasmaphosphate)}{(urinecreatinine/plasmacreatinine)}
\]

When the TRP is less than 0.86, the TmP/GFR can be calculated directly as follows:

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TmP/GFR = TRP \times Plasmaphosphate
\]

Normal reference range for this age group is 2.9-6.5 mg/dl (6).

In this patient the biochemical finding is normal calcium, low phosphate, low 25 hydroxy vitamin D, normal parathormone, increased alkaline phosphatase, low fractional tubular reabsorption of phosphate and tubular reabsorption of phosphate for corrected glomerular filtration rate is only 1.54 mg/dl.

Autosomal Dominant hypophosphatemic rickets is due to Fibroblast Growth Factor 23 gene mutation which causes renal phosphate wasting. Fibroblast Growth Factor 23 is produced from bone cells. It acts on FGF receptor-1 in proximal tubular cells and inhibits phosphate reabsorption.

Autosomal recessive hypophosphatemic rickets -1 is due to DMP-1 (Dentin matrix acidic phosphoprotein-1) mutation and 2- is due to ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1 gene) mutation.

**CONCLUSION**

In this patient symptoms of rickets since 5 years of age and initially does not respond to vitamin D therapy. Clinical, biochemical and radiological findings suggestive of X-linked hypophosphatemic rickets.

**REFERENCES**