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CASE STUDY

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ABSTRACT

Rickets develops when growing bones fail to mineralize. In most cases, the diagnosis is established with a thorough history and physical examination and confirmed by laboratory evaluation. Rickets has types include (Nutritional rickets, Congenital Rickets of prematurity, Vitamin D resistance (type I and type II), Neoplastic rickets, Hypophosphatemic rickets, Drug-induced rickets. In our case study we aimed to establish the challenge primary care physicians while diagnosis and treating hypophosphatemic rickets. This case focus on a study done in the hospital within one-year duration with detailed personal patient's family and medical history supported with x r-rays, lab investigations, and flow charts. We summarize the way of diagnosis and treatment for XLHR (X-linked hypophosphatemic rickets).

KEYWORDS: Neoplastic rickets, Hypophosphatemic rickets, Drug-induced rickets.

Case details

Personal history

A male patient, Fahad Sultan, 5 years old, 5th kid in his family from Thadik, KSA of moderate socioeconomic standard.

Complaint

Deformity of both Lower limbs, Inability to walk with bone pain.

Present history

The patient was well and quite till the age of 3.5 years old when he complained of lower limb pain with mild deformity and limping, making his parents started looking for medical advice at orthopedic consultation in Thadik hospital and the doctor noticed both lower limbs

deformity so he preferred referring them to a pediatric consultation which ordered special investigations.

The patient was diagnosed vitamin D deficiency rickets case of after the investigations was done.

The pediatrician recommended to take a course of vitamin D, calcium and L-carnitine for about 3 months' duration showing minimal improvement, then 3 months later multivitamin was added to the given course for 6 months' duration then repeated vitamin D level which became normal.

Patient complained of recurrent attacks of bony pain mainly in both lower limbs with inability to walk, so the parents repeated multiple courses of vitamin D with mild improvement for 3.5 years' duration without medical consultation.

One month ago, due to the recurrence of symptoms, the patient was referred to a pediatric consultant which was reinvestigated.

* There is no history of delayed teething or chest deformity, but only there is history of prominent head.
* There is no history of recurrent chest infection regarding fever, cough or dyspnoea.
* There is No history suggestive of bone trauma or infection nor history suggestive of arthritis regarding redness, swelling.
* There is no history suggestive of chronic liver disease regarding jaundice, oedema and bleeding nor history suggestive of chronic renal disease regarding dysuria, polyuria oliguria or haematuria.
* There is also no history suggestive of malabsorption regarding prolonged diarrhoea, weight loss nor history of prolonged drug intake.
* There is no history suggesting other system affection

Past history

* There is no history of recurrent chest infections
* No previous admission at hospital
* No operations or blood transfusion
* There is no history of drug intake other than oral vitamin D3 intake (cholecalciferol), calcium and L-carnitine since the age of 3.5 years old.

Family history

* There is negative consanguinity.
* Oher siblings are 2 males and 2 females are normal.
* No history of similar condition and other diseases in the family.

Developmental history

- ✓ There is no history suggesting gross motor delay as patient sit alone at the age of 6 months, crawled at 9 months, walked at 12 months.
- ✓ No history suggesting delayed fine motor development.
- ✓ There is history of normal mental development
- ✓ Normal vision, hearing and speech development.

Dietetic history

Mother gave dietetic history as her child was breast and artificial feed, given as needed, for about 10-15 minutes, each fed from one breast and given artificial formula until signs of satisfaction after fed in the form of sleep and gain wait.

Weaning also was adequate as it started at 6 months by introduction of cereals and vegetables, this followed by introduction of new types of food with increasing their amounts and by the age of 1 year, he was eating family diet with sometimes breast fed.

Vaccination history

Patient received all regular and compulsory vaccines at proper time without any complications.

Examination

General Examination

The patient is conscious, cooperative, oriented for time place and person with no abnormal face, average built and no special decubitus. There is mild pallor with no cyanosis or jaundice.

Blood pressure: 95/65 Temp: 36.7 Respiratory rate: 25 pulse: 98 bpm

Weight: 19.5 kg (25th centile)

Height: 114.5 cm (just below 3rd centile)

Head circumference: 55 cm

Head examination

- Large head
- Depressed nasal bridge
- Prominent forehead
- Dental caries
- No alopecia

Limb examination

There is broadening of both wrists and ankles

Lower limb deformity in the form of Genu valgum

Positive Marfan sign

Chest examination

Rachitic rosaries

Mild chest deformity in the form of pectus carinatum

Abdominal examination

No hepatosplenomegaly or umbilical hernia

No spine deformity

Investigations

Investigations done at 04/01/2020

Alkaline phosphatase: 1185 ---- 557

Ionized calcium 1.3 (1.2-1.36)

Total calcium 10.7 (8.8-10.8)

Serum phosphorous: 3.1 low (4-8)

Recent investigations done in the last two months

CBC was normal (Hemoglobin 13, WBCs 6.6 with normal differential count, platelet 250)

ESR: 1st hour 10

CRP: negative

Bone profile

Serum calcium: 9.6 ---- 10

Ionized calcium: 1.27 --- 1.34

Alkaline phosphatase: high 670--- 764

S phosphorous: 3.3 low (4-8) --- 3.2

25 OH vitamin D: 29.05

PTH: 30.6 pg. /ml (15-65)

Serum magnesium: 2 mg/dl (1.7-2.1)

Serum Creatinine: 0.51 (0.5-1)

Serum Urea: 19 (11-39)

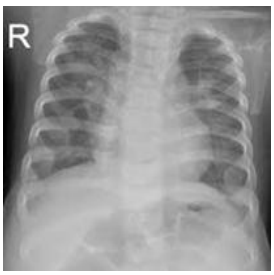
Serum Uric acid: 2.8 (2-5)

ABG: normal

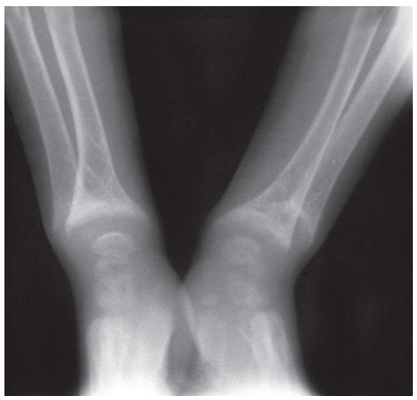
Urine analysis: normal

Urine amino gram: normal pattern

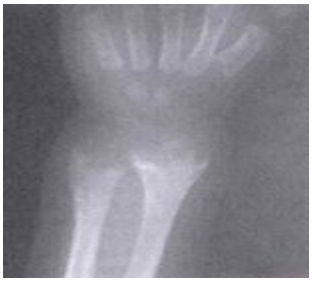
Calcium in 24 hr. urine: 98 normal (up to 6 mg/kg body weight)



Rachitic rosary refers to expansion of the anterior rib ends at the cost chondral junctions and is most frequently seen in rickets as nodularity at the cost chondral junctions.



X-Ray knees: Broad epiphysis, Cupping and osteopenia.



Anteroposterior radiograph of the wrist with rickets demonstrates cupping and fraying of the metaphyseal region.

How to suspect a case of rickets?

Clinical

- Bone deformities (Forearm deformities, bow legs (genu varum) or knocks knees (genu valgum)
- rachitic rosary
- Growth retardation
- frontal bossing of the skull
- craniotabes (soft skull bones)
- delayed tooth eruption
- widened fontanelles
- fractures

Extra skeletal manifestations (weakness and hypotonia of proximal muscles, irritability, hypo calcemic seizures, tetany and laryngospasm)

Radiological

Widening of the growth plates, cupping, fraying, osteopenia.

Laboratory

Serum calcium, phosphorous and alkaline phosphatase

25(OH)vitamin D and PTH

Serum Ca, P, PTH, vitamin D; may be:

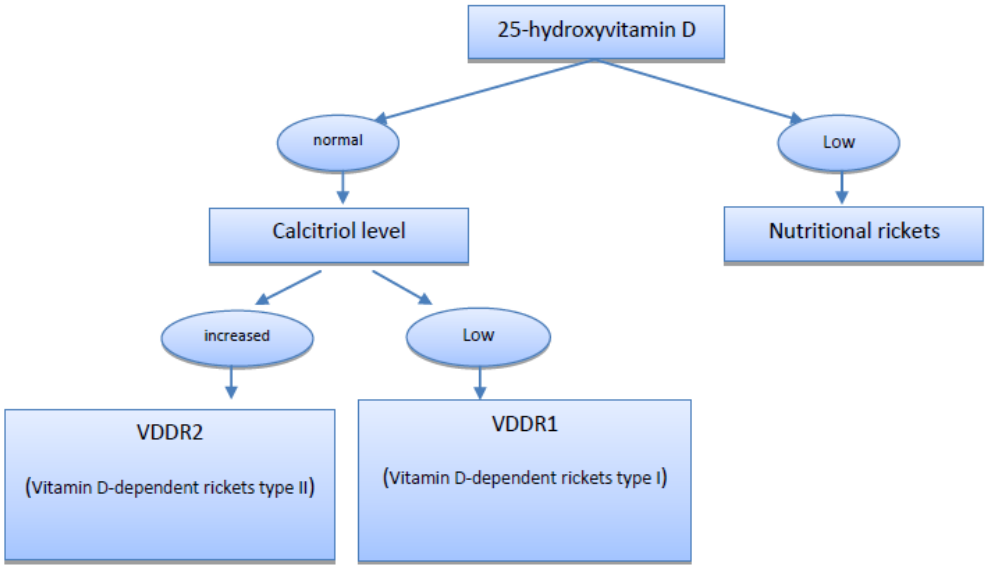
1-Calcipenic rickets

Increase PTH, normal or reduced ca, reduced phosphate.

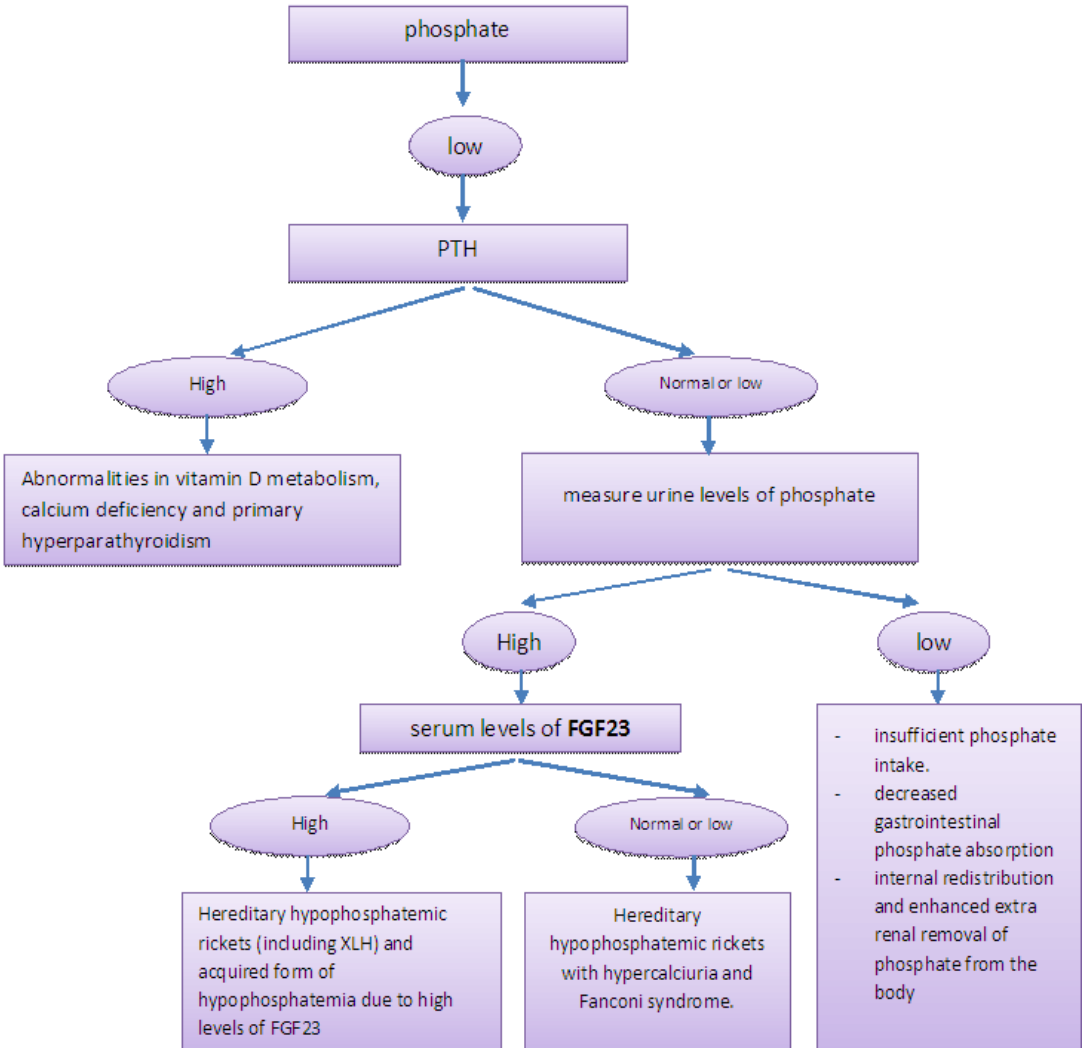
2-Phosphopenic rickets

Normal PTH, reduced phosphate.

1- Calcipenic rickets



2- Phosphopenic rickets



So our patient with Bony pain, lower limbs deformity, normal calcium, normal parathyroid hormone, normal ABG, hypophosphatemia and received multiples courses of vitamin D →refractory rickets so the diagnosis is **Hypophosphatemic Rickets**

X-Linked Dominant Hypophosphatemic Rickets (XLHR)

XLHR is the most common form of hypophosphatemic rickets with an incidence of 1:20,000. It results from the inactivating mutations in the PHEX gene (the phosphate regulating gene on the X chromosome), expressed in osteocytes and odontoblasts. These determine an increased synthesis and secretion of FGF23, which regulates renal tubular resorption of (Pi) inorganic phosphate.

Increased FGF23 levels result in renal wasting of Pi at the proximal tubule level and reduced 1-alpha-hydroxylation of 25-OH vitamin D.

XLHR manifests as a spectrum of disorders, from hypophosphatemia alone to short stature. Frontal bossing is one of the initial clinical signs, appearing as early as six months of age.

As the children start walking, other signs become evident including coxa vara, genu valgum, or varum. Stunted growth may be a revealing sign in up to 14% of cases; therefore, any leg bowing whether or not associated with poor statural growth should be investigated.

Tooth abscesses or facial cellulitis on apparently non-carious teeth are common and suggest poor dentin mineralization. Unlike vitamin D deficiency, craniotabes, rachitic rosary, and fractures are rare. Finally, recent studies have shown higher incidence of cranio-vertebral abnormalities, especially cranio-synostosis and Chiari type 1 malformation.

Biochemical hallmarks of XLHR include:

1- hypophosphatemia,
2- increased ALP,
3- elevated serum levels of FGF23.

A diagnosis of XLHR should be considered in the presence of

1- clinical and/or radiological signs of rickets
2- impaired growth velocity
3- Hypophosphatemia associated with Pi renal wasting without vitamin D or Ca deficiency.

Renal tubular reabsorption of phosphate is calculated with the following formula

$$TRPi = \left(1 - \frac{PO_4\,(U) \times Cr\,(S)}{PO_4\,(S) \times Cr\,(U)}\right) \times 100$$

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TRP in XLH is 60%

Normal TRP exceeds 90%

Where possible, diagnoses should be confirmed by genetic testing

Any first-generation family member of a patient with XLHR should be investigated for XLHR. However, approximately one-third of reported patients have a negative family history for XLHR; in these patients, a mutational analysis for the PHEX gene is also recommended. If genetic analysis is not available, elevated plasma levels of FGF23 and/or a positive family history for XHLR can be used to support the diagnosis.

Treatment

Recommended treatment of XLHR includes oral supplementation of active vitamin D (calcitriol or alfacalcidol) and phosphate.

The effective doses vary from 20–60 mg/kg body weight daily for phosphate supplements, and 20–30 ng/kg for calcitriol or 30–50 ng/kg for alfacalcidol.

Recommended treatment should be continued until the completion of growth. Adverse effects including nephrocalcinosis and secondary hyperparathyroidism can occur.

Nephrocalcinosis, which happens subsequently to urinary calcium loss, is reported in 30–70% of patients with XLHR; therefore, periodic urinary Ca monitoring is recommended.

Secondary hyperparathyroidism is the consequence of prolonged stimulation of the parathyroid by FGF23 and Pi supplementation, and most frequently occurs in patients not treated with calcitriol or alfacalcidol. Thus, to prevent it, PTH levels during conventional treatment should be maintained within 10–65 pg/mL.

An important novelty in the treatment of XLHR was the introduction of burosumab, a recombinant human monoclonal IgG1 antibody that targets FGF23, restoring (renal Na+/phosphate) Napi co-transporter. Evidence-based European guidelines recommend

burosumab treatment in children older than one year and in adolescents with growing skeletons in the presence of:

(1) radiological evidence of overt bone disease;

(2) disease refractory to recommended therapy;

(3) complication related to recommended therapy; and

(4) noncompliance to recommended therapy.

Recommended starting dose is 0.4 mg/kg subcutaneously every two weeks. Burosumab is generally a well-tolerated drug; injection site reactions are the most frequently reported side effects. Other possible adverse reactions include headache, vomiting, pyrexia, and extremities pain. Despite its benefits, various aspects of burosumab in XLHR therapy are yet to be explored and further studies are needed.

Management of our patient

Patient started oral phosphate therapy (sodium phosphate) and alfacalcidol drops.

Alfacalcidol 30-50 ng/kg/day

Oral phosphate 20-60 mg/kg/day

In spite of good compliance on oral phosphate therapy , phosphorous level decreased 3.3 → 3

So that, our patient was admitted and received Intravenous phosphate (Glycophos) organic phosphate (sodium glycerophosphate) in a dose: 1-1.5 mmol /kg/D

He received IV glycophos and serum phosphorous increased to 3 then 3.5 mg/dl

Oral phosphate dose increased so our patient discharged for follow up.

With improvement of the symptoms (bony pain and limping)

Monitoring

Calcium, Phosphate, Alkaline Phosphatase

Urine calcium /creatinine every 3-4 months and PTH annually

Autosomal Dominant Hypophosphatemic Rickets (ADHR)

ADHR is caused by activating missense mutations in FGF23 that make the protein resistant to the cleavage by the FGF23-targeting converting enzyme, leading to an increased expression of FGF23 and phosphaturia.

Clinical findings are similar to those in XLHR, especially in childhood onset, whereas bone pain, weakness and pseudo fractures are more common in adolescence. In addition, several studies have shown an association between iron deficiency ad severe disease manifestations.

Treatment of ADHR is similar to that of XLHR and includes:
Pi (inorganic phosphate) and calcitriol administration.
Iron therapy should be prescribed if iron deficiency is present.

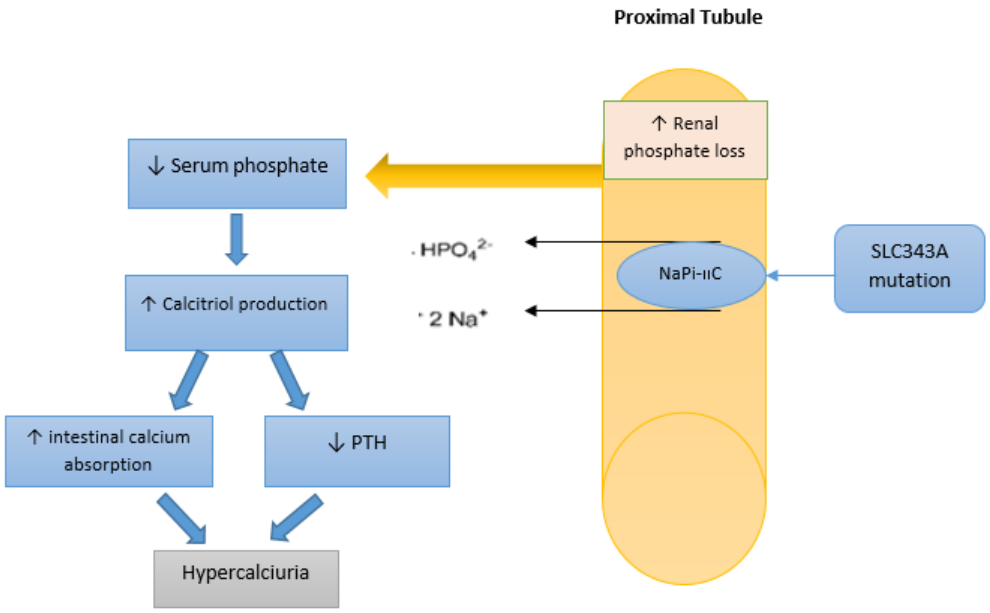
Autosomal Recessive Hypophosphatemic Rickets (ARHR)
Mutations can affect ARHR, different phenotypes of the disease.
Autosomal recessive hypophosphatemic rickets type 1 (ARHR1) is caused by homozygous loss-of-function mutations in the DMP1 gene. (a noncollagenous bone matrix protein expressed in osteoblasts and osteocytes). DMP1 has a role in osteocyte proliferation and in the downregulation of FGF-23 and hence loss of its function will augment FGF-23 activity, explaining renal phosphate loss and hypophosphatemia.

Autosomal recessive hypophosphatemic rickets type 2 (ARHR2) is a skeletal condition that is characterized by rickets, bone pain, bone deformities. It occurs because of a loss of function mutations in ectonucleotide pyrophosphate/phosphodiesterase 1 gene (ENPP1), which regulates matrix vesicle pathway and pyrophosphate-mediated bone mineralization. The results are impaired bone mineralization, idiopathic infantile arterial calcification, ossification of the posterior longitudinal ligament of the spine, and insulin resistance. Clinical, laboratory, and radiological findings of patients with ARHR are similar to those of XLHR patients.

Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH)
Hereditary hypophosphatemic rickets with hypercalciuria is a rare autosomal recessive disorder characterized by the presence of hypophosphatemia secondary to renal phosphate wasting, radiographic and/or histologic evidence of rickets, limb deformities, muscle weakness, and pseudo fractures in childhood are common presenting features dental abnormalities are not usually reported.

Hereditary hypophosphatemic rickets with hypercalciuria results from the loss of function mutations in the SLC34A3 gene that encodes NaPi-2c (sodium phosphate cotransporter), with consequent tubular Pi wasting and hypophosphatemia.

Bone pain



In contrast to other variants of inherited hypohosphatemic rickets, FGF-23 level is normal and 1,25-dihydroxy vitamin D levels are elevated.

These patients also exhibit hypercalciuria, which predisposes them to nephrolithiasis.

Treatment

Supplementation with oral Pi (inorganic phosphate) may heal rickets and represents the mainstay of (HHRH) Hereditary hypophosphatemic rickets with hypercalciuria.

In contrast with other forms of hypophosphatemic rickets, calcitriol administration should be avoided because it increases the risk of developing nephrocalcinosis/recurrent nephrolithiasis.

Rickets is a disease of infants and children that disturb normal bone formation(ossification) leading to failure to mineralize bone. But Several diseases can result in disorders of bone mineralization.

Include:

1-Rickets

2-McCune Albright syndrome

3-Renal diseases (renal osteodystrophy, fanconi syndrome)

4-Tumor induced osteomalacia

5-Hypophosphatasia

6-Osteogenesis imperfect

Category	T score
Normal	Not more than 1.0 standard deviations (SD) below the young adult mean.
Osteopenia	Between 1.0-2.5 SD below the young adult mean.
Osteoporosis	More than 2.5 SD below the young adult mean.
Sever or established Osteoporosis	More than 2.5 SD below the young adult mean with fracture.