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Case Series

# Rickets: 2 Forms of Presentation

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## Abstract

Rickets is caused by a failure of osteoid to calcify in a growing person. We present two cases of rickets: the first one in a 3 years old girl with short stature and varus knees. Plasma phosphorus was low, with high levels of alkaline phosphatase and parathormone. She has great loss of phosphorus in urine but amino acids, bicarbonate, serum 1,25-dihydroxyvitamin D3 showed normal levels. Skeletal x-ray revealed signs of rickets particularly in the wrist. The DNA study detected missense mutations R179Q in FGF23 gene. This result confirmed the diagnosis of autosomal dominant hypophosphatemic rickets (ADHR). The another case is a 2 years old boy with polyuria, polydipsia, failure to thrive, retardation of motor development at 10 month of age, microcytic hypochromic anemia, hypoglycemia, hypophosphatemia and increase levels of AST/ASL and alkaline phosphatase at 18 months, with signs of rickets at 20 months. Metabolic and skin biopsy study confirmed the diagnosis of Tyrosinemia type I with no activity of fumarylacetoacetase in the skin fibroblast.

***Keywords:*** *Rickets; Short Stature; Polyuria; Polydipsia*

## Introduction

Rickets is caused by a failure of osteoid to calcify in a growing person. Vitamin D deficiency reduce intake of calcium or phosphorus, Fanconi syndrome, may produce rickets.

In the vitamin D deficiency, we have hypocalcemia that stimulates excess secretion of parathyroid hormone but phosphorus levels remain low. Alkaline phosphatase showed very high levels in this situation.

Hypotonia, craniotabes, frontal bossing and delays the closure of the anterior fontanelle, bowlegs and knock-knees are observed in most patients with clinical signs of rickets. If rickets occurs at a later age, thickening of the skull develops. The x-ray showed cupping and flaring of the metaphysis. In the chest, we observe the so-called rachitic rosary along the costochondral junctions. The weakened ribs pulled by muscles also produce flaring over the diaphragm, which is known as Harrison groove. The sternum may be pulled into a pigeon-breast deformity.

In more severe cases in children older than 2 years, we can observe kyphoscoliosis. The ends of the long bones demonstrate that same knobby thickening. At the ankle, palpation of the tibia malleolus gives the impression of a double epiphysis (Marfan sign). Because the softened long bones may bend, they may fracture on one side of the cortex (greenstick fracture).

Differential diagnosis of vitamin D dependent deficiency are mainly with hypophosphatasia, Jansen syndrome, a rare autosomal dominant form of short-limbed dwarfism in which infants present with metaphyseal chondroplasia and hypophosphatemic vitamin D-resistant rickets.

When we have clinical suspicious of rickets, we need to check the following blood test: calcium, phosphorus, alkaline phosphatase, parathyroid hormone, 25-hydroxy vitamin D and 1,25-dihydroxyvitamin D.

Radiographic examination is important to confirm the typical metaphysis widening and cupping because of their exaggerated normal concavity and irregular calcification. Along the shaft, the uncalcified osteoid causes the periosteum to appear separated from the diaphysis and we can find also osteopenia. Treatment for rickets may be administered in a single-day dose of 15,000 mcg (600,000U) of vitamin D divided into 4 or 6 oral doses. In nutritional rickets, the phosphorus level rises in 4 days and radiographic healing is visible in 6 - 7 days. If severe deformities have occurred, orthopedic correction may be required after healing [1-3].

## Cases Reports

### Case 1

A 3 y old girl was sent to our pediatric outpatient because of short stature and suspect of metaphases dysplasia. Until two years of age the stature was normal for the age, in the 50 percentiles. Later decreased to less than 5 percentiles, with weight and head circumference over 95 percentiles. The growth velocity was normal at the first year of life and increased only 5.5 cm at the second year. On physical examination, we found short stature, macrocephaly and varus knees. Normal psychomotor development. The analyses showed normal karyotype and thyroid function. Plasma phosphorus was low, with high levels of alkaline phosphatase and parathormone. She has great loss of phosphorus in urine but amino acids, bicarbonate, serum 1,25-dihydroxyvitamin D3 showed normal levels. Skeletal x-ray revealed signs of rickets particularly in the wrist (Figure 1).

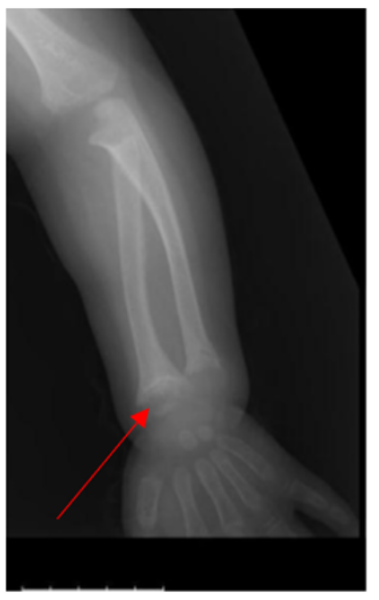

***Figure 1:*** *Cupping and flaring of the metaphysis.*

We started treatment with calcitriol and Joulie solution with recovered of her growth, increasing 10.5 cm in 13 months. Her varus knees normalized during this period (Figure 2). The DNA study detected missense mutations R179Q in FGF23 gene.

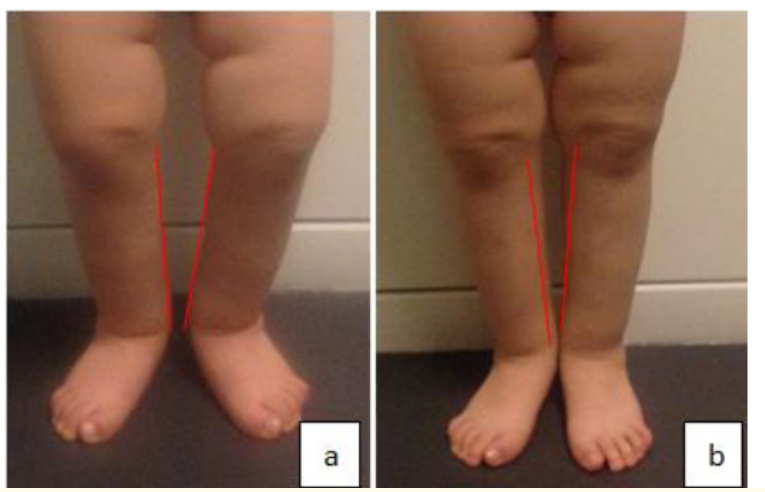


***Figure 2:*** *Varus knees improvement: before (a) and after(b) 1 year of treatment with calcitriol and Joulie's solution.*

This result confirmed the diagnosis of Autosomal dominant hypophosphatemic rickets (ADHR), characterized by isolated renal phosphate wasting, hypophosphatemia and inappropriately normal 1,25-dihydroxyvitamin D3 (calcitriol) levels. The family history and gene screening of both parents were negative. This means that our case was sporadic presentation.

## Case 2

A 2 years old male, with history of polyuria, polydipsia, failure to thrive, retardation of motor development at 10 month of age, microcytic hypochromic anemia, hypoglycemia, hypophosphatemia and increase levels of AST/ASL and alkaline phosphatase at 18 months, was diagnosed rickets and respiratory distress at 20 months. His private doctor start treatment with vitamin D3 and iron. At 24 months, because the symptoms were more severe, he admitted in hospital for investigation. On physical examination, revealed malnourished child (weight - 7 kg - < P3), complaining at manipulation, tachypnea and global retractions, bilateral rough breath sounds with rales in the pulmonary bases, abdominal distention, liver palpable 8 cm below the costal edge at the midclavicular line, oral and perineal candidiasis, retardation of motor development (not seating without support and not standing with support) and rickets signs (anterior fontanelle 2,5 x 3,5 cm with soft boards, rachitic rosary, wrists and ankles enlargement) (Figure 3 and 4).

The laboratory and imagiologic evaluations showed abnormal results for: Pi 1,5 mg/dL (N: 2,5 - 6,4); AST 54 U/L (N: 1 - 37); γ-GT 685 U/L (N: 5 - 18); Alkaline phosphatase 1650 U/L (N: 54 - 280); Total Bilirubin 1,75 mg/dL (N: 0,1 - 1,0); α-fetoprotein > 30000 UI/mL (N: 0,0 - 5,0) Urine: glucose ++++, protein +++. Tubular reabsorption of phosphorus: 45,3% (N: 80 - 95%). Blood gases: pH: 7,242; $pCO_2$: 62,3 mmHg; $pO_2$: 78,5 mmHg; $HCO_3$: 26,6 mmol/L; BE: 2,5 mmol/L; $SatO_2$: 95%. Chest and abdominal CT revealed: "Osseous deformity of chest, ribs "with" wavy aspect, more prominent in the postero-lateral region of the inferior half of left hemichest, with depression and image of several costal fractures. Liver moderately increased, heterogeneous, with little, spread, hypodense nodules, translating hepatopathy. Kidneys enlarged. Limbs x ray revealed signs of rickets (Figure 5).

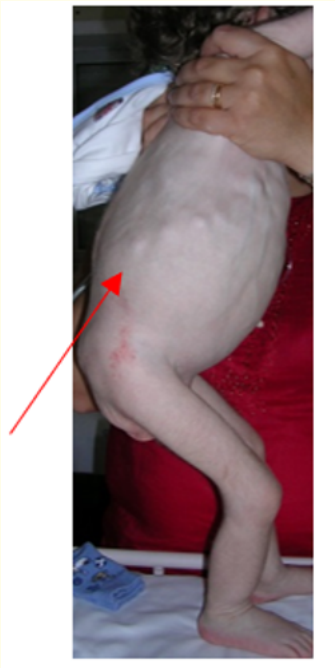

***Figure 3:*** *Rachitic rosary along the costochondral region.*

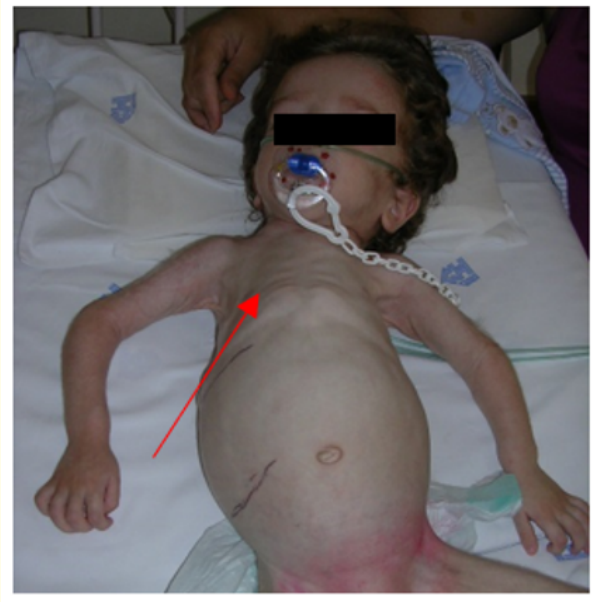

***Figure 4:*** *Harrison groove and pigeon breast deformity.*

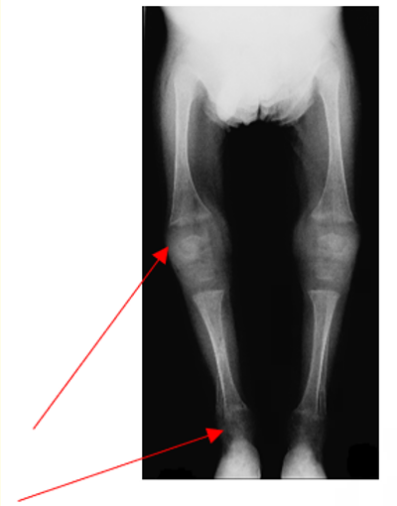

***Figure 5:*** *The x-ray showed signs of rickets.*

Metabolic and skin biopsy study confirmed the diagnosis of Tyrosinemia type I: Plasma - Tyrosine - 145 µmol/L (N: 25 - 60), Phenylalanine - 44 µmol/L (N: 28 - 68), Methionine- 34 µmol/L (N: 4 - 44). Urine - Generalized Hyperaminoaciduria, presence of great amount of the acids derived from tyrosine metabolism, of succinyl acetoaceticacid and succinyl acetone. No activity of fumarylacetoacetase was found in the skin fibroblast.

Hereditary tyrosinemia type I is a metabolic disorder, inherited as an autosomal recessive trait, caused by deficiency of fumarylacetoacetase (FAH), the last enzyme in the tyrosine degradation pathway.

## Discussion

In case 1, Patients frequently present with bone pain, rickets, and tooth abscesses. In contrast to X-linked dominant hypophosphatemic rickets (XLH), ADHR shows incomplete penetrance, variable age at onset (childhood to adult), and resolution of the phosphate-wasting defect in rare cases. Other forms of hypophosphatemic rickets include an autosomal recessive forms, ARHR1, caused by mutation in the DMP1 gene on chromosome 4q21 and ARHR2, caused by mutation in the ENPP1 gene on chromosome 6q22-q23. An X-linked dominant form is caused by mutation in the PHEX gene, and an X-linked recessive form is caused by mutation in the CLCN5 gene.

Our case after one year of treatment responded well to association of calcitriol and Joulie solution. The most two important clinical respond was the normalization of varus knees and catch-up growth velocity. The laboratory and radiologic changes will take time to normalize. The child onset has much better prognosis than in the adult form. There are reports that the final stature will achieve the target growth for the mean parental height. No family history was found. The risk for next pregnancy is low because our case was a sporadic presentation [1-3].

In case 2, the patient has signs of rickets secondary to Fanconi syndrome. We start treatment with NTBC: 1 mg/kg/day, bid, hypoproteic/hypercaloric diet, restricted intake of tyrosine and phenylalanine, oral supplement with vitamin D, phosphate, potassium and sodium citrate, calcium. After 4 months, showed general and nutritional improvement (η1135gr in weight and 2 cm in length), seats and stands with support and the size of the liver was reduced.

In presence of any abnormality of the kidneys and/or liver function or of a bone disorder in a child or adolescent, we should considered tyrosinemia type I. Only with an early diagnosis, a diet low in phenylalanine and tyrosine and NTBC therapy can promptly initiated, in the hope of preventing renal complications and early death from liver failure or hepatocarcinoma [4].

In both cases, clinical signs of rickets were found. The correct diagnosis and treatment are the two main reasons they both recovered well after some months. The genetic counselling and prenatal diagnosis of the future pregnancy can be offered to the both couples.

## Conclusion

Nowadays is rare we have patients with rickets classic signs secondary to low intake of vitamin D. When we observe a child with rickets and short stature, associated with low level of phosphorus in plasma and high levels of alkaline phosphatase and parathormone, we need to consider autosomal dominant hypophosphatemic rickets. On the other hand, when we find a patient with rickets, polyuria, polydipsia and failure to thrive with general microcytic hypochromic anemia, hypoglycemia, hypophosphatemia, increase levels of AST/ASL and alkaline phosphatase, tyrosinemia type I should be the consider too.

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