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## Hypophosphatemic Rickets with Hypercalciuria

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A new syndrome, hereditary hypophosphatemic rickets with hypercalciuria (HRH), was recently described in closely related members of a Bedouin tribe in Israel(1,2). This condition is characterized by renal phosphate leak resulting in hypophosphatemia with an

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appropriate elevation of blood levels of 1,25 dihydroxyvitamin D, increased intestinal calcium absorption and hypercalciuria. HRH is a distinct condition and must be differentiated from the patients of classic hypophosphatemic rickets. The rarity of this condition prompts us to report the clinical and laboratory features and response to therapy in two such patients.

### Case Reports

*Case 1: A 6-year-old girl of unrelated healthy parents was referred for evaluation of long standing rickets. She was well till the age of one and a half years when bowing of legs and difficulty in walking were noticed. The bony deformities chiefly involved the lower limbs and progressively increased. At the age of 5 years she started complaining of bone pain, mainly at the pelvic girdle and legs, and developed a waddling gait. On examination the height was 102 cm (<5th percentile) and weight 17 kg*

(10th percentile). The lower extremities were disproportionately short and showed anterolateral bowing of thighs, genu varum and double malleoli. Widening of wrists and rachitic rosary were also present. The dentition was normal. X-ray examination of long bones showed features of rickets with metaphyseal cupping and fraying and generalized demineralization.

The results of the investigations are shown in *Table I*. Examination of multiple 24-hour urine samples showed marked hypercalciuria ranging from 208-266 mg (12.2-15.6 mg/kg per day). The blood levels of calcium, creatinine, electrolytes, pH, bicarbonate and osmolality were within normal range and those of phosphate markedly reduced (2.2-2.4 mg/dl). The serum levels of al-

kaline phosphatase ranged between 1000-1200 IU/L (normal 400-700 IU/L).

Urine examination did not show protein, glucose or excessive aminoaciduria. The fractional excretion of bicarbonate was 2% and ammonium chloride loading resulted in the urinary pH of 5, excluding the diagnosis of renal tubular acidosis. The tubular reabsorption of phosphate and maximal tubular phosphate reabsorption /glomerular filtration rate (TmP/GFR) were 70% and 2.1 mg/dl, respectively (*Table I*), being low for age. The blood level of parathyroid hormone (mid-molecule) was 5 ng/dl (normal: less than 27 ng/dl).

The patient was diagnosed to have HRH and treated with oral phosphate supplements in the dose of 50 mg/kg/

**TABLE I**-Investigations in Patients with Hypophosphatemic Rickets and Hypercalciuria

Investigation	Case 1	Case 2
Blood		
Calcium (mg/ dl)	10.0 - 11.2	8.6 -11.0
Phosphate (mg/ dl)	2.2- 2.6	1.8 - 2.1
Alkaline phosphatase (IV /L)	1000-1200	2000-2200
Creatinine (ing/ dl)	0.5	0.4
Bicarbonate (mEq/L)	21.8	22.3
pH	7.41	7.44
24 hour urine calcium (mg/kg)	12.2-15.6	8.2-16.5
Tubular reabsorption of phosphate (%)	70	30
TmP/GFR (mg/dl)*	2.1	1.2
Fractional excretion of bicarbonate (%)	2	1
Ultrasound abdomen	Nephrocalcinosis absent	Nephrocalcinosis absent

\* TmP /GFR= Maximum tubular reabsorption rate for phosphate per dl glomerular filtrate; normal values  $4.6 \pm 0.5$  mg/ dl(3).

day in 5 divided doses. Within 8 weeks the bone pain disappeared and radiological features of rickets were absent after 7 months of treatment. On follow up, 30 months later, her height was 118 cm (25th percentile). The blood levels of phosphate gradually rose to 3.6-3.7 mg/dl and alkaline phosphatase reduced to 600 IU/L. The 24-hour urine Ca excretion was high (7-9 mg/kg per day) and the TmP/GFR reduced at 3.0 mg/dl.

*Case 2:* A 4-year-old boy showed bony deformities and difficulty in walking since the age of one and a half years. He was the fourth born child of a non-consanguineous marriage; the parents and the siblings were apparently normal. He was treated with oral vitamin D in a dose of 600,000 IU on two occasions with no apparent improvement. His height was 80 cm (< 5th percentile) and weight 11 kg (5th percentile). There was frontal bossing, widened wrists, rachitic rosary and genu valgum. The rest of the systemic examination including dentition was normal.

The results of investigations are shown in *Table 1*. X-ray examination showed features of active rickets. Blood levels of phosphate were markedly low and alkaline phosphatase elevated; those of calcium, urea, electrolytes, creatinine, pH and bicarbonate were normal. Urine examination showed a pH of 5.5 and marked hypercalciuria (urine calcium 8.2-16.5 mg/kg per day). The TmP/GFR was low for the age (1.2 mg/dl). Following bicarbonate administration the difference between urine and blood pCO<sub>2</sub>, was 36 mm Hg and the fractional excretion of bicarbonate was 1%, thereby excluding the diagnosis of renal tubular acidosis. A diagnosis of

HRH was made and the child was treated with oral phosphate supplements in a dose of 60 mg/kg/day. Within 4 months the child had gained 4 cm in height and started walking. The level of blood phosphate rose to 2.8 mg/dl and alkaline phosphatase was 1900 IU/L. A repeat X-ray examination showed healing of rickets.

### Discussion

Both these patients showed short stature, refractory rickets, increased renal phosphate clearance and hypophosphatemia. In addition they had marked hypercalciuria with normal levels of blood calcium. There was no evidence of any other renal tubular dysfunction. Despite absence of data on blood levels of 1,25 dihydroxyvitamin D, these features are highly suggestive of the diagnosis of HRH. Treatment with oral phosphate supplements led to healing of rickets, improved growth rate and decrease in levels of blood phosphate.

HRH has previously been described in two Israeli kindreds(2,4), and a few sporadic cases from Japan(5) and north America(6). Family studies suggest that the mode of inheritance is autosomal recessive(2,4). Siblings of patients with HRH may show evidence of idiopathic hypercalciuria with no bone disease(2,4). HRH is distinct from classical familial hypophosphatemic rickets where the mode of inheritance is usually X-linked dominant and the urinary calcium excretion is normal or low.

The most significant difference between HRH and the classical X-linked hypophosphatemic rickets is in blood levels of 1,25 dihydroxyvitamin D.

Phosphate deficiency is a potent and direct stimulus for renal 25-hydroxyvitamin D 1-alpha hydroxylase activity(7). Hypophosphatemia, in HRH therefore, results in marked increase in blood levels of 1,25 dihydroxyvitamin D(1,2,4-6). Elevated levels of this active vitamin D analog promote intestinal calcium and phosphorus absorption which, in turn, leads to hypercalciuria. However, in patients with the classical hypophosphatemic rickets there is a defective response of renal 1-alpha hydroxylase to hypophosphatemia(8). This results in levels of 1,25 dihydroxyvitamin D which are inappropriately low in relation to reduced serum phosphorus in the latter.

Long term phosphate supplementation in both our patients with HRH resulted in rapid improvement of clinical and radiographic abnormalities. The blood levels of phosphorus increased and alkaline phosphatase returned to normal.

It has been suggested that long term supplementation with phosphates may induce enteric hyperoxaluria and development of nephrocalcinosis in patients with X-linked hypophosphatemic rickets(9). A recent report has not confirmed the hypothesis of phosphate-induced hyperoxaluria in patients with HRH(10). Phosphate therapy is therefore, considered safe in these patients. Therapy with vitamin D is, however contraindicated since it may further increase intestinal absorption of calcium and aggravate hypercalciuria with a risk of nephrocalcinosis.(11).

It is possible that HRH is underdiagnosed due to its similarity to

X-linked hypophosphatemic rickets. Measurement of levels of serum 1,25 dihydroxyvitamin D may not be possible in most centers in this country. However, an awareness of the condition should prompt measurement of urinary calcium excretion in all patients with hypophosphatemic rickets. Patients with HRH respond satisfactorily to long term phosphate supplementation and therapy with vitamin D analogs must be avoided.

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## Multifocal Skeletal Tuberculosis Presenting as Osteitis Skull and Atlantoaxial Dislocation

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Although skeletal tuberculosis is still frequent in many parts of the world, multifocal bone involvement in tuberculosis is rare. It is reported that 4.6% to 10% of skeletal tuberculosis is multifocal(1,2). Osteitis of skull with associated

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multiple cerebral tuberculoma with atlantoaxial dislocation of tubercular etiology manifesting in a child has not been reported in the English literature to the best of our knowledge. The present report describes a 14-year-old female who presented with the above findings with histopathological proven skeletal tuberculosis and reviews the literature on multifocal skeletal tuberculosis.

### Case Report

A 14-year-old female presented with a swelling in the occipital region associated with localized headache for the last 5 months. The swelling was initially pea size and progressively increased and finally burst discharging pus leaving a sinus. Two months prior to admission the swelling was excised by a local doctor but it recurred and increased in size. There was no history of preceding trauma. Ever since the appearance of swelling, patient had malaise, low grade fever with evening rise and progressive weight loss. One month after the swell-