Hereditary hypophosphataemic rickets: report of a family from the Indian subcontinent

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Summary

Nutritional deficiency continues to be an important cause of rickets in the underdeveloped and developing parts of the world. In the western hemisphere, predominantly non-nutritional forms of rickets and osteomalacia are now seen. In this report we discuss a family with X-linked hypophosphataemic rickets from the Kashmir region of the Indian subcontinent (which is an uncommon entity here).

Keywords: hypophosphataemia; rickets

Nutritional deficiency is no longer an important cause of rickets in the western world, although it still is in India.¹ Rickets and osteomalacia can occur in association with a variety of disorders of proximal renal tubular function; these disorders have in common increased renal clearance of inorganic phosphates and hypophosphataemia with a normal glomerular filtration rate. Primary hypophosphataemic rickets is characterised by severe short stature and rickets in association with hypophosphataemia and hyperphosphaturia and usually has an X-linked mode of inheritance.² In this report we describe a family with hypophosphataemic rickets where we believe the mode of transmission is X-linked dominant. A Medline search for the last 30 years revealed only one such family described from India so far.³

Case report

Index case

A 3-year-old girl, 5th in birth order was born of a full term normal delivery at home. She had failed to thrive since the age of 2 years. There was no suggestion of any chronic systemic disease. Examination revealed a well-nourished girl, height 79 cm, weight 10 kg (expected 50th percentiles for her height and weight: 94 cm and 10.5 kg, respectively). Upper segment lower segment ratio was 1.23. She had frontal bossing, widening of epiphyseal ends of long bones with knock knees, rachitic rosary, Harrison's sulcus and pigeon chest deformity. Family history was significant (figures 1 and 2). Of her four siblings, the three males (E-G) were normal while the other girl (B) was affected. Her father (C) and paternal uncle (D) were affected while her mother was normal. Her paternal grandmother, who had died 10 years

earlier, was also reported to have had short stature and leg deformities.

Other affected cases

Elder sister (B): Although she had a chronological age of 16 years, there had also been a failure of linear growth since the age of 3 years, and she had gradually developed deformities of the lower limbs. She had attained menarche at age 14 years and was having regular cycles. Examination revealed a height of 134 cm and weight of 35 kg (expected 50th percentiles were 157 cm and 47.5 kg, respectively). She had mild pallor, knock knees, mild anterior bowing of legs, widening of epiphyses and pigeon chest deformity. Systemic examination was normal.

Father (C): Aged 48 years, he had developed progressive deformity of upper and lower limbs during his childhood. He was 140 cm tall (corresponding to a height age of 11 years) and weighed 42 kg (consistent with his present height). He had multiple bony deformities including bowing of legs, bending of forearms, lumbar kyphoscoliosis. Systemic examination was normal.

Figure 1 Family photograph showing short stature and anterior bowing of legs in affected individuals (reproduced with their permission)

Figure 2 Family pedigree, identifying individuals affected

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Figure 3 X-ray of the wrist showing changes of rickets at the epiphyseal end of long bones

Figure 4 X-ray of the lower limbs showing bowing of long bones with multiple previous fractures

Paternal uncle (D): Aged 35 years, he was 137 cm tall, consistent with a height age of 10 years. He weighed 38 kg. He had knock knees, anterior bowing of both legs and lumbar scoliosis.

Full blood count, serum and urinary calcium, and ammonium chloride test were normal in all subjects, and none of them had proteinuria or glycosuria. Radiological screening revealed advanced changes of rickets/osteomalacia in the affected subjects (figures 3 and 4). There was a mild elevation of total alkaline phosphatase in the affected subjects, all of whom had persistent hypophosphataemia. Mean serum phosphorous was 1.9 mg/dl in affected members and 4.5 mg/dl in unaffected ones (normal range, 3.0–4.5 mg/dl). Our index case, surprisingly, had high serum 25-hydroxyvitamin D (> 100 ng/ml) and undetectable (<5 pg/ml) 1,25-dihydroxyvitamin D. This biochemical abnormality was reproducible. Serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were normal in other affected as well as unaffected subjects (table).

Discussion

In India, malnutrition continues to be the leading cause of rickets, although other causes of rickets are increasingly recognised.⁴ In this study we describe a family in which all the female children had advanced changes of rickets/osteomalacia while the male children were spared. Their father and paternal uncle were affected while their mother was normal. Historically, their paternal grandmother had also been affected. Thus, it is evident that transmission of the disease is X-linked dominant.

In developed nations nutritional rickets, primarily due to vitamin D deficiency, has almost been eliminated as a result of fortification of some foods. By the 1940s vitamin D deficiency was no longer considered to be an important cause of osteomalacia and rickets. In North America the most common form of inherited rickets is X-linked dominant hypophosphataemic rickets.⁵ This entity was first described by Albright and co-workers in 1937.⁶ The phenotypic trait of hypophosphataemia is transmitted on the X-chromosome. Patients with familial hypophosphataemic rickets are recognised by marked rickets with hypophosphataemia and hyperphosphaturia coupled with increased serum alkaline phosphatase with normal or slightly reduced serum calcium; urinary phosphate excretion is high, despite hypophosphataemia indicating a defect in renal tubular reabsorption of phosphate. Phosphaturia is unassociated with either aminoaciduria, glucosuria, bicarbonaturia, or kaliuria.⁷ Serum levels of immunoreactive parathyroid hormone are either normal or mildly increased.⁸ Serum levels of 25-hydroxyvitamin D are normal whereas

Table Biochemical investigations

Subject	Serum Ca (mg/dl)	Serum P (mg/dl)	Serum ALP (U/l)	Urinary Ca (mg/day)	Serum 25(OH)D (ng/ml)	Serum 1,25(OH) ₂ D (pg/ml)
A	9.6	1.9	721	194.6	>100	<5.0
B	9.01	2.1	587	205.7	9.4	18.0
C	8.23	1.6	373	118.4	28.0	19.0
D	8.8	2.3	721	110.2	32.0	17.0
E	9.36	4.5	371	214.2	36.2	14.0
F	8.15	4.2	347	197.3	39.0	31.0
G	8.30	4.1	307	227.2	25.7	26.0
Normal range	9–10.5	3–4.5	30–120	100–400	8–80	16–65

ALP: alkaline phosphatase

1,25-dihydroxyvitamin D levels are either normal or low.^{9 10} Our index case had elevated 25-hydroxyvitamin D levels with undetectable 1,25-dihydroxyvitamin D. The only logical explanation for this biochemical abnormality could be a concomitant sporadic 1 α -hydroxylase deficiency.

Children affected with this disorder progressively develop lower limb deformities once they begin to walk and bear weight. The deformities progressively worsen in an otherwise well-nourished and healthy child. The rate of linear growth is at first normal and then slowed, ultimately resulting in short stature.²

On the basis of restriction fragment polymorphism studies in several kindred of X-linked hypophosphataemia, the mutant gene has been mapped to the short arm of the X-chromosome (Xp22.1). A candidate gene called PEX that exhibits homology to a family of endopeptidase genes has been identified and several mutations, including deletions, frame shifts and splice-junction defects, have been reported.¹⁰

Learning points

- hypophosphataemia is an uncommon cause of rickets in India
- subjects show changes characteristic of deforming rickets with severe compromise of height
- hyperphosphaturia is present despite hypophosphataemia
- combination of oral phosphate and 1,25-dihydroxyvitamin D3 significantly improves the clinical course of disease in children

Treatment of this disorder continues to be a therapeutic challenge. Administration of 1,25-dihydroxyvitamin D and phosphates significantly improves the clinical course of this disease in childhood.¹¹ A similar therapeutic regimen results in significant clinical and histomorphometric improvement in adults with this disorder.¹²

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