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CASE REPORT

X-LINKED HYPOPHOSPHATEMIC RICKETS: A CASE REPORT

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ABSTRACT

Hypophosphatemic rickets is a type of hereditary rickets characterized by persistent hypophosphatemia and hyperphosphaturia. The most predominant type is inherited in an x-linked fashion and caused by mutation in the gene encoding the phosphateregulating endopeptidase homolog X-linked (PHEX) which causes deficient mineralization of structures such as bones and teeth. The pathophysiological defect in XLH is speculated to cause an increase in a circulating phosphate regulating hormone termed phosphatonin (fibroblast growth factor 23 is the primary phosphatonin) which leads to parathyroid hormone-independent phosphaturia. We here describe a patient 30 years old male with genu varum, which presented with fragility fracture in lower limb and diagnosed as X-linked dominant hypophosphatemia (XLH) with osteomalacia after thorough history, examination, radiological and various blood tests.

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INTRODUCTION

XHR (X-linked hypophosphatemic rickets) is a dominant inherited disorder with a prevalence of approximately one case per 20,000 live births (Alizadeh Naderi and Reilly, 2010). It is characterized by wasting of phosphate from the kidneys which lead to chronic hyperphosphaturia and hypophosphatemia, which may or may not be associated with normal or low levels of 1,25 (OH)vitamin D3. This phosphorus-wasting disorder affects the bone metabolism which causes rickets in pediatric patients and osteomalacia in adults (Quarles, 2003; Rowe, 2000; Cho*et al*., 2005; Bielesz *et al*., 2004). It is caused by one or more circulating factors termed as phosphatonins, which promote phosphate excretion and impair bone mineralization rather by a defect in kidneys. In XHR, hyperphosphaturia is caused by mutation in the PHEX gene (phosphate regulating endopeptidase on X-chromosome), which is identified on Xp22.1and is mainly expressed in bone and teeth (Quarles, 2003; Rowe, 2000; Cho *et al*., 2005; Bielesz *et al*., 2004; Rowe, 2004; De Beurand Levine, 2002; Saggese, and Baroncelli, 2000). The principal phosphatonin involved in pathogenesis of XLH is fibroblast growth factor 23 which act as phosphaturic agents, by inhibiting phosphorus reabsorption in the proximal tubules, through sodiumand phosphateco-transporters inhibition. Untreated XHR is associated with growth retardation, bone deformities and fragility fractures.

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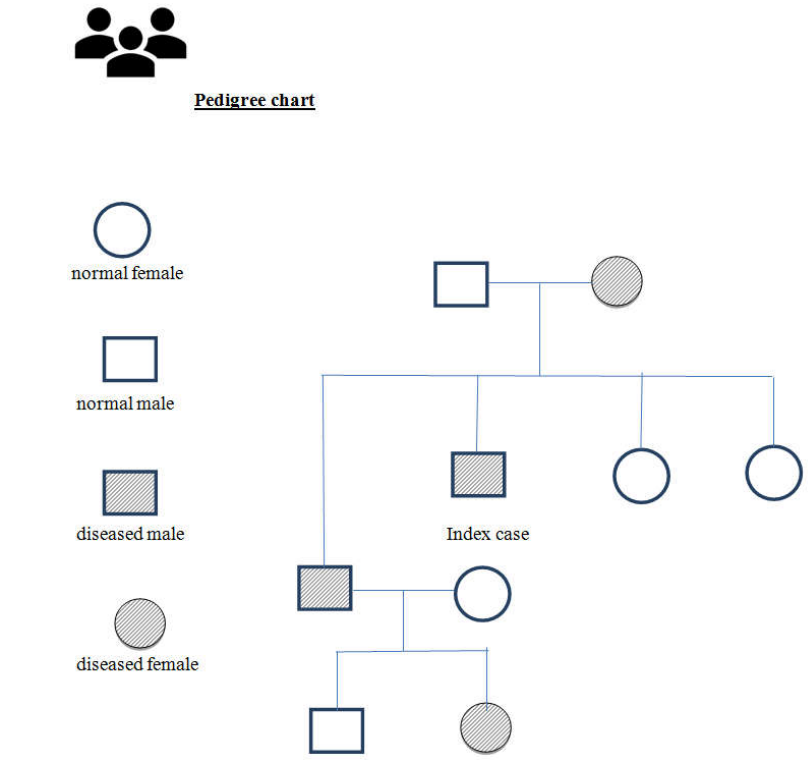
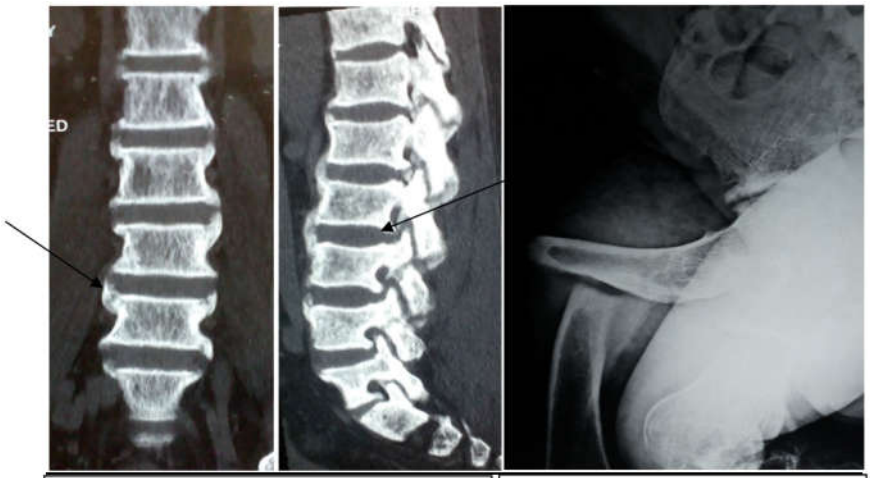
Case presentation

This case report describes the clinical, radiological, andbiochemical features of hypophosphatemic rickets in a patient of 30 years old who came to the endocrinology clinic with a chief complaint of deformity of lower limbs since childhood and wound in right upper thigh since last 2 months. There was history of fall 3 years back when he developed fracture in left thigh. Patient again fall from bed 2 months back and injured his right thigh. There is history of similar complaints of deformities of limbs and fragility fractures in other family members (as shown in pedigree chart below). He had no history of polyuria, dysuria, jaundice, recurrent chest infections or recurrent attacks of diarrhea and not on long term anticonvulsant drugs. Though his milestones of development were normal, her linear growth was not satisfactory as compared to that of other adult of his age. Exposure to sunlight was adequate as he used to play along with other children in open air during his childhood. On examination, patient was bed ridden, genu verum deformity was present in lower limbs with compound fracture of right thigh. His pulse rate was 82/min, bp-110/70 mm hg and temperature were normal. Rest of the systemic examination was within normal limits. Laboratory investigations showed normal complete blood counts and normal urine examination, normal serum calcium (Ca++) level of 9.4 mg/dl (8.8-10.8 mg/dl), low serum phosphate of 2.2 mg/dl (4-7 mg/dl), while alkaline phosphatase was 300 iu/l which was much higher. Liver and renal functions are within normal limits with serum creatinine of 0.8 mg/dl.





X-ray Lumber sacral spine (AP & Lateral view) showing calcifications of ligaments

X-ray right hip and thigh (AP view) showing deformed bone and fracture right femur

The parathyroid hormone (PTH) level was raised to 106.90 pg/ml (7-53 pg/ml) and the levels of 25 hydroxy vitamin D3 was normal 70.24 nmol/l. 24-hour urine examination showed marked hyperphosphaturia and its level was 3366.5 mg/dl (400-1300 mg/dl) with Fractional excretion of phosphate 48.2%. 24-hour urinary creatinine was 24.20 mg/dl (14-26mg/dl) within normal limit. 24-hour urinary calcium was 96.00 mg/dl (100-300mg/dl) within normal limit. Urine for bence jones proteins was negative. Patient had normal blood gas analysis. All parameters of electrolytes were normal. Urine test showed no glucosuria and aminoaciduria. Usg neck was normal. Dexa scan T-score at lumber spine was 7. Serum fibroblast growth factor 23 (FGF-23) levels were found to be raised. Based on history of deformity of extremities, fragility fractures, presence of same complaints in family members and laboratory findings consistent with familial hypophosphatemic rickets with x-linked dominant inheritance. Treatment with tablet calcitriol 0.25 microgram once daily and oral phosphorus 500 milligram thrice daily was started.

DISCUSSION

Rickets is a disease which is characterized by defective mineralization of osteoid matrix of bone during growth that leads to the development of bone defects and the presence of short stature. Osteomalacia is defined as the disorder of bone tissue characterized by inadequate or delayed mineralization of osteoid in mature cortical and spongy bone. Common causes of osteomalacia usually divided into disorders of calcium deficiency or vitamin d deficiency or of phosphate deficiency. The main causes of hypophosphatemic rickets are the familial rickets and one of the most frequent is familial X-linked hypophosphatemic rickets (XHR) (Wharton and Bishop, 2003; Rootand Diamond 2002; Garg and Tandon, 1999; Winters*et al*., 1958). The XHR is characterized by an increased secretion of phosphate from kidneys which leads to a hypophosphatemia but with normal calcium levels. In the XHR, the FGF-23 levels, whose function is to inhibit sodium phosphate cotransporter in proximal renal tubule and 1α-hydroxylase enzyme, are

increased and leads to hyperphosphaturia (Quarles, 2003; Segawa *et al*., 2002; Murer *et al*., 2004; strewler, 2001; riminucci *et al*., 2003). This increase in FGF-23 is produced by a deficit of PHEX protein, a transmembrane protein that promotes FGF-23 cleavage in smaller and two inactive peptides, encoded by the gene PHEX, located on chromosome Xp22.1 (Quarles, 2003; Saggeseand baroncelli, 2000; Bowe *et al*., 2001). The diagnosis of XHR is based on a consistent medical history and physical examination, radiological evidenceof rachitic disease, compatible laboratory values and a family history consistent with XHR or the demonstration of PHEX mutations (Dixon *et al*., 1998).The main goal of treatment in adults are to reduce pain symptoms, to reduce the extent of osteomalacia (the abundance of mineralized osteoid present in the skeleton), and to improve fracture healing. Treatment includes calcitriol and phosphorus in selected adults with XLH like patients with spontaneous insufficiency fractures, as in our case. Treatment is usually individualized for each patient depending on age, body weight, parathyroid status, and renal function. The major risks of long-term therapy with calcitriol and phosphorus are similar in both children and adults, like hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis and potentially, chronic kidney disease. So, a careful monitoring is required to minimize these risks. During the first year of treatment at stable doses, we repeat biochemical evaluation every 3 to 4 months. As osteomalacia heals with treatment the requirements for calcitriol and phosphorus may decrease abruptly, so frequent monitoring is essential especially in the first year of treatment. It is important to detect these changesas early as possible to avoid prolonged hypercalcemia or hypercalciuria. Beyond the first year we generally monitor treated adult patients every 6 to 9 months.As noted, the goals of treatment in adults are to reduce pain and the extent of osteomalacia and to improve fracture healing or surgical recovery. Radiographs can be used to objectively assess healing of fractures or recovery after surgery.

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