Vitamin D-resistant rickets (X-linked hypophosphataemic rickets)

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Summary
Rickets is a condition affecting the growing skeleton, causing demineralisation of bone, growth disturbance and deformity. Most forms of the disease are due to alterations in vitamin D homeostasis. Vitamin D-resistant rickets, however, is due to a disorder of renal phosphate reabsorption. X-linked hypophosphataemic rickets (XLHR) is the commonest inherited form of these disorders and this article will concentrate on this variant of the disease, summarising its clinical features and pathophysiology and outlining the goals and methods of treatment.

Introduction
The term rickets broadly covers a variety of disease states with differing aetiology but a common pathophysiological mechanism. This leads to a relative decrease in calcium or phosphate or both, the scale of which produces a failure of normal mineralisation of bone and epiphyseal cartilage causing skeletal deformity. Rickets occurs in the growing skeleton; its equivalent in the mature skeleton is osteomalacia.

Historically, rickets was one of the earliest syndromes to be defined. In 1645, Daniel Whistler described the "English disease, commonly known as rickets". The first classic medical text on the subject is attributed to Francis Glisson in 1650. Pommer in 1885 fully described and defined the histological changes occurring within the epiphyseal plate and cortical and medullary bone.

The links to diet and environment were made at the beginning of the 20th century. During the 1920s the first of the vitamin Ds were isolated and by the end this decade rickets and osteomalacia were considered to be deficiency diseases curable by the addition of vitamin D to the diet.

In the 1930s it became apparent that some individuals with rickets or osteomalacia were resistant to even massive doses of supplemental vitamin D. Three such patients were described by Albright et al. in 1937 as a clinical entity. They named the condition "rickets resistant to vitamin D," and postulated the cause was a chemical lesion in the renal tubule.

Further types of renal tubular syndromes and hypophosphataemic rickets were described following this, and in 1958 Winters et al. first described a hereditary cause of vitamin D-resistant rickets with a sex-linked-dominant inheritance. This X-linked hypophosphataemic rickets

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(XLHR) is the commonest form of inherited rickets affecting 1 in 20,000 of newborns.\(^3\)

**Clinical features**

The clinical features of XLHR vary with the age on onset. Presentation is usually in the second year of life; occasionally, it may be much later, such as early adulthood.

Generally there is an impairment of growth, although weight may be normal or even higher than age-matched normals. Growth disturbance can be variable and affect the upper body as much as the lower limbs.

Although major milestones may be delayed, muscle weakness, tetany and convulsions are unusual, as the serum calcium is usually normal. A degree of hypotonia may affect gait or the onset of walking. The child may be clumsy, inattentive and irritable; the wrists and ankles may be thickened and the tibias bowed. Fractures are uncommon.

In the child with florid disease the findings are more striking and males are more severely affected. It is unclear whether XLHR compromises life expectancy.\(^3\)

**Facial features**

The effects of rickets on the facial skeleton include flattening of the skull, frontal bossing (due to the delay in closure of the anterior fontanelle), caput quadratum (hot-cross-bun skull), cranial synostosis, delayed dentition, enamel hypoplasia and severe dental caries. Sensorineural hearing loss can also occur in the adult.

**Spine and torso**

The chest may demonstrate enlargement of the costal cartilages (rachitic rosary), indentation of the lower ribs where the diaphragm inserts (Harrison's groove) and pectus carinatum. The spine may become kyphotic and adults can develop spinal stenosis.

**Limbs**

Distal femoral and tibial bowing causes genu valgum or varum. Ankles, knees and wrists are typically thickened. Bone and large joint pains are common and often disabling. The risk of a slipped upper femoral epiphysis is increased in the young adolescent.\(^4\) Ectopic ossification of tendinous
insertions and in periarticular regions have been reported in adults. Thigh pain in adults can be caused by incomplete femoral stress fractures (Looser’s zones).

**Investigations**

**Biochemical tests**

The biochemical traits of XLHR are hypophosphataemia (with an increased renal phosphate leakage) and high alkaline phosphatase. Serum calcium and 25-OH-vitamin D are normal. The diagnosis is thus made on these findings, with the clinical features of rickets and a positive family history if relevant. Diagnosis in the newborn can be difficult because phosphate levels can remain normal for up to 9 months. Alkaline phosphatase levels begin to rise from 4 months of age, confirming the diagnosis in those with a family history of the disorder and radiographic changes.

**Radiology**

The characteristic skeletal changes seen in rickets occur early with widening of the physeal plates and cupping and fraying of the adjacent metaphysis. The bones most commonly affected are the proximal and distal tibia, the distal femur and the distal radius and ulna (Figs. 1 and 2). Although changes around the knee become more pronounced as the child grows, the wrist changes tend to be minimal with thickening and slight loss of movement.

Looser’s zones are common and represent incomplete stress fractures which heal with demineralised callus. Affected sites include the humerus, femur, pubic ramus and scapula.

Rickets due to disturbances of vitamin D homeostasis produce secondary hyperparathyroidism, leading to osteopenia and subperiosteal bone resorption. This does not occur in XLHR where thickened cortices and more dense trabecular bone are sometimes seen.

**Aetiology and histopathology**

The pathogenesis of XLHR is not fully understood. Transport of phosphate is defective across renal proximal tubule cells. The disorder is inherited as an X-linked-dominant trait. Recently, mutations in the PHEX gene on chromosome
Xp22.1 have been isolated.\textsuperscript{6} This gene encodes for an endopeptidase that has been postulated to be important in the breakdown of FGF23, a fibroblast growth factor protein, known to inhibit renal phosphate reabsorption.

Histologically the condition is characterised by the presence of demineralised osteoid and in the growing child proliferation of chondroid hypertrophic cells at the sites of endochondral bone growth.

**Treatment**

The treatment of XLHR requires a multidisciplinary approach involving both medical and orthopaedic specialists, preferably in centres with the necessary experience in the timing and type of treatment best suited to the individual. It is widely agreed that a key to maximising success of treatment is the early recognition of the condition. Early treatment leads to the best chance of reducing the likelihood of significant deformity and short stature. Indeed the diagnosis should be considered in any child presenting with angular deformity of the limbs and delayed growth.\textsuperscript{9} Without a correct diagnosis, early and perhaps inappropriate major surgery is doomed to failure. The goals of treatment are to prevent or correct limb deformity before skeletal maturity and to achieve optimal height.\textsuperscript{3}

Treatment ideally begins in infancy with oral 1, 25-dihydroxyvitamin D3 and phosphate supplementation. Radiological resolution of the defects in skeletal growth and improvement of the histological abnormalities can be observed in compliant patients. Whether final height can be influenced using medical therapies remains controversial.\textsuperscript{3} Complications of supplementary treatment include hypercalciuria, leading potentially to nephrocalcinosis, and hypercalcaemia due to increased calcium absorption. Following corrective surgery or fracture patients who are non-weight bearing immobilisation hypercalciuria and hypercalcaemia may develop unless supplementation is stopped temporarily.

Orthopaedic evaluation should occur at least yearly in childhood and twice yearly during the adolescent growth spurt. Limb bracing, epiphysiodesis and osteotomies may have to be considered if deformity is progressive or symptomatic, ideally delayed until adolescence.\textsuperscript{9,10} Osteotomies are usually bilateral and are fixed with no plates or external fixation (Figs. 3–5).

Newer treatments remain controversial and experimental. Recombinant Growth hormone (rhGH) is known to enhance renal phosphate reabsorption and has been shown to increase plasma phosphate concentration and height scores but also exacerbates upper to lower segment ratios.\textsuperscript{11}

**References**