Growth hormone treatment in a child with X-linked hypophosphataemic rickets

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INTRODUCTION

X-linked hypophosphataemic (XLH) rickets is characterised by low serum phosphorus, relative 1,25-dihydroxyvitamin D3 (1,25(OH)₂D3) deficiency and rickets.¹ It is caused by mutations in the phosphate-regulating gene on the short arm of X-chromosome (PHEX). The conventional treatment of XLH rickets includes the administration of phosphate and calcitriol; however, treated patients usually present with a short stature. Therefore, additional coexistent defects, such as growth hormone (GH) deficiency, are under debate.² The pathogenesis of short stature is probably multifactorial. Affected patients usually show normal GH secretion. Long-term GH treatment along with conventional therapy improves linear growth.³ It has also been shown to promote renal phosphate conservation resulting in a better metabolic control.

CASE REPORT

A 12-year-old male child presented with stunted growth, bowing of long bones, and waddling gait (Figure 1). In addition, he suffered from recurrent dental abscesses. The family history was positive, as the mother suffered from rickets and disproportionate growth failure with a final height of 150 cm. Clinical examination revealed short stature (112 cm, i.e. <2 SD) and an elevated upper segment/lower segment (US/LS) ratio (1.4/1). His head circumference was 52 cm and arm span was 119 cm. He showed radiological signs of rickets with metaphyseal widening, fraying and cupping of the ulna, distal femur and bow legs (Figures 2A and B). Laboratory investigations revealed normal serum calcium (9.3 mg/dL), low serum phosphorus (2.2 mg/dL;

N: 2.9–5.4) and elevated alkaline phosphatase (1,065 U/L; N: 200–495) levels. Renal function tests were normal (serum urea: 18 mg/dL, creatinine: 0.6 mg/dL and eGFR ≥75 mL/minute/1.73 m²) and there was no features of metabolic/renal acidosis (arterial blood gas pH: 7.4, bicarbonate: 24 mmol/L). Phosphate wasting was confirmed by reduced renal reabsorption of phosphate (TRP: 50%), and based on hypophosphatemia, increased serum alkaline phosphatase, radiological sign of rickets and a family history compatible with X-linked dominant inheritance, a diagnosis of XLH rickets was made.

The child was started on oral phosphate (20 mg/Kg/day of neutral-phos powder) supplementation and calcitriol [1,25(OH)₂D3] (0.5 µg/day). Growth hormone (rhGH) treatment was commenced after one month, with 0.03 mg/Kg/day and administered as daily subcutaneous injections. During the 12-month rhGH treatment, the patient was assessed at trimonthly intervals (at 3, 6, 9 and 12 months). Deformities were assessed clinically and by obtaining standard clinical photographs at 0 and 12 months. At rhGH onset, the height Z-score was –4.8

Figure 1 Short stature with bowing of lower limbs in a 12-year-old boy with X-linked hypophosphataemic rickets.

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Figure 2 Radiograph of both knee and wrist showing bowing, hypomineralization, cupping, fraying and spreading of metaphyses of the end of long bones. Genu vara is also seen.

and the child was in pre-pubertal stage (Tanner 1–2). The height Z-score increased significantly during rhGH and was -2.4 (130cm) at the end of the treatment. The Z-score for sitting height to total height ratio increased during the study from 1.4 to 1.8 at 12 months, suggesting that body disproportion increased during GH treatment. The patient had hypophosphatemia prior to rhGH therapy. However, at 12 months, the serum levels had returned to normal (3.6mg/dL). The patient underwent surgery (osteotomy) for lower limb deformities during the 15-month study period. No rhGH-associated side effects were observed; the blood count, thyroid function and HbA_{1c} remained normal throughout the study. No catch-down growth was observed during the six months' follow-up period.

DISCUSSION

X-linked dominant hypophosphataemic rickets (Online Mendelian Inheritance in Man [OMIM] No. 307800) is a monogenic disease with variable expressivity of clinical features, namely rickets with bone deformities, dental abnormalities and shortness of stature. This disease was originally described by Albright in 1937, and the delineation of its X-linked inheritance was demonstrated by Winters in 1958.^{4,5} A major therapeutic breakthrough occurred at the end of the 1970s, when a new therapeutic strategy was introduced, combining oral phosphate and calcitriol, or 1 α -hydroxyvitamin D3 and its synthetic analogue.⁶ This treatment considerably improved bone mineralisation and reduced or prevented bone deformities, thus reducing the need of surgical osteotomy. It also had a clear beneficial impact on dental health. However, its effect on growth remained controversial; some authors reported improvements in growth velocity, but others observed inconstant or non-significant catch-up growth.^{3,7} Furthermore, this treatment is associated with significant adverse effects such as secondary and tertiary hyperparathyroidism, hypercalcaemia, hypercalciuria, and nephrocalcinosis.⁸ Hence, long-term compliance with this regimen is difficult and the results of the treatment unsatisfactory.

Growth hormone has been used in addition to conventional treatment in those with compromised growth and suboptimal metabolic control to improve longitudinal growth and decrease phosphate requirements.^{9–12} Growth hormone acts as a phosphate sparing agent and thus lower the dosage of phosphate required during treatment. This is more effective in improving biochemical defects, ensuring compliance and minimising adverse effects such as nephrocalcinosis. None of the patients showed significant advancement in bone age during the study period and it is therefore possible that the gains in height will result in improved adult height. Body disproportion increased in pre-pubertal patients, suggesting that their modest growth response to rhGH was mostly spinal growth. In some patients lower limb deformities advanced and patients required surgery. Hence, careful orthopaedic follow-up is recommended during GH treatment. Previous studies have shown that GH increases renal tubular phosphate reabsorption and the serum concentration of 1,25(OH)₂D3, suggesting that GH, through IGF-I, is involved in phosphate homeostasis and in 1 α -hydroxylation of 25-OH-D3 in proximal renal tubule of kidney.^{9,10} Zoidis et al¹³ showed that IGF-I increased PHEX expression in bone and sodium-dependent phosphate co-transporter mRNA expression in kidney and suggested that IGF-I increases circulating phosphate concentration through these two mechanisms.

Our findings are in accordance with previous observations, which suggest that GH improves renal phosphate reabsorption and thus results in increased serum concentrations of phosphate. Growth improved in pre-pubertal patient and no significant catch-down growth was observed during the post-treatment follow-up, suggesting that the gain in height was not merely a temporary peak in growth velocity. However, a longer follow-up would be needed to confirm this observation. Also, improved growth was associated with deterioration of lower limb deformities and body disproportion increased.

CONFLICTS OF INTEREST

None identified.

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