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Disproportionate growth following long-term growth hormone treatment in short children with X-linked hypophosphataemia

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Abstract Three short prepubertal children with X-linked hypophosphataemia were treated with 1 IU recombinant human growth hormone (rhGH)/kg per week sc in addition to calcitriol and phosphate supplementation over a period of 3 years. Improvement of height standard deviation score (SDS) ranged from 1.0–1.7 SD based on an increase in sitting height of 1.5–2.9 SD, whereas subischial leg length improved only slightly by 0.3–0.9 SD. In all three patients, renal phosphate threshold concentration increased slightly and transient hyperparathyroidism was noted.

Conclusion Treatment of stunted children with X-linked hypophosphataemia is effective in improving growth velocity, but appears to aggravate the pre-existent disproportionate stature of such children.

Key words X-linked hypophosphataemia · Short stature · Growth hormone · Disproportionate growth · Secondary hyperparathyroidism

Abbreviations *GFR* glomerular filtration rate · *GH* growth hormone · *rhGH* recombinant human growth hormone · *TmP/GFR* renal threshold phosphate concentration · *XLH* X-linked hypophosphataemia

Introduction

Most patients with X-linked hypophosphataemia (XLH) present with short stature. Treatment with calcitriol and phosphate supplementation may result in improvement of rickets and growth [3, 5], but complete catch-up growth is only rarely observed [9, 13]. Friedman et al. [4] suggested that the most severely stunted children manifest resistance to the growth promoting effect of calcitriol and phosphate and stated the need for new treatment strategies. In a short-term study, Wilson et al. [15] gained evidence that exogenous growth hormone (GH) therapy may be useful in XLH by demonstrating that GH treatment over 6 months increased serum phosphate concentration and growth velocity. We report the 3-year results of recombinant human growth hormone (rhGH) treatment in three children with XLH and short stature who had been treated with calcitriol and phosphate supplementation for several years.

Methods

We investigated three children with classical XLH (positive family history) with an age of 8.8 years (patient 1), 9.4 years (patient 2) and 11.1 years (patient 3) at start of rhGH treatment. Patient 1 was female, patients 2 and 3 were male siblings. Anthropometric data are given in Table 1. The children were treated with calcitriol and phosphate supplements for at least 5 years. They had a prescription of fixed individual doses of calcitriol (1.0–1.5 μg/day) and of oral phosphate supplementation (0.8–2.1 g/day) during the year prior to rhGH treatment. The individual prescription was not changed during the entire study period. GH deficiency was excluded by a GH stimulation test with L-arginine (peak GH serum concentration > 10 μg/l) and by normal serum GH night profiles (≥ 3 peaks > 10 μg/l). 1 IU rhGH/kg per week (Genotropin, Pharmacia, Stockholm, Sweden) was given by daily s.c. injections in the evening.

Table 1 Growth and biochemical data of three children with X-linked hypophosphataemia treated with rhGH over 3 years (*S* serum, *U* urine, *IGF-1* insulin-like growth factor 1, *IGFBP-3* insulin-like growth factor binding protein 3, *iPTH* intact parathyroid hormone (normal values: 1–6pmol/l))

	P[a]	Start rhGH	1 year rhGH	2 years rhGH	3 years rhGH
Pubertal stage[b]	1	PH1, B1	PH1, B1	PH1, B2	PH3, B3
	2	PH1, G1	PH1, G1	PH3, G3	PH4, G4
	3	PH1, G1	PH2, G1	PH3, G2	PH4, G4
Height SDS	1	–5.4	–4.3	–4.1	–4.0
	2	–2.0	–1.2	–0.7	–0.3
	3	–2.0	–1.2	–1.0	–1.0
Subischial leg lenght SDS	1	–5.5	–4.7	–4.6	–4.6
	2	–2.2	–1.6	–1.4	–1.4
	3	–2.3	–1.6	–1.9	–2.0
Sitting height SDS	1	–4.1	–2.8	–2.4	–1.9
	2	–1.6	–0.0	0.7	1.3
	3	–1.4	–0.6	0.0	0.1
Bone age (years)	1	4.8	5.5	6.6	10.8
	2	8.0	9.6	11.5	13.0
	3	9.0	10.1	12.3	13.5
S-IGF-1 SDS		–0.5 (–1.0 to –0.1)	0.8 (0.5–1.3)	1.0 (0.6–1.2)	0.9 (0.7–1.3)
S-IGFBP-3 SDS		0.0 (–0.3–0.2)	1.0 (0.9–1.3)	1.1 (0.8–1.2)	1.0 (0.7–1.4)
S-iPTH (pmol/l)		3.6 (3.2–3.8)	7.5 (2.7–7.8)	3.4 (3.1–8.4)	3.6 (2.9–8.9)
S-Calcium (mmol/l)		2.4 (2.3–2.5)	2.5 2.4–2.5)	2.4 (2.3–2.5)	2.5 (2.4–2.5)
S-Phosphate (mmol/l)		0.7 (0.5–0.8)	1.1 (1.0–1.1)	0.8 (0.8–0.9)	0.7 (0.6–0.8)
S-Alkaline Phosphatase (U/l)		455 (433–718)	930 (919–1026)	985 (953–1308)	959 (653–1230)
GFR (ml/min/1.73 m^2)		140 (123–149)	135 (119–136)	141 (126–154)	148 (131–158)
U-Calcium excretion (μmol/day/kg)		211 (67–213)	91 (80–201)	92 (70–191)	77 (70–155)
U-Phosphate excretion (mmol/day/kg)		1.61 (1.05–1.86)	1.19 (1.14–1.39)	0.80 (0.55–1.04)	0.93 (0.67–1.04)

[a] Patient number
[b] According to Tanner

The patients were examined at 3-monthly intervals. The laboratory methods used are described in detail elsewhere [12] and included radioimmunoassays for insulin-like growth factor 1, IGF-binding protein-3, and intact parathyroid hormone. A morning urine sample was used for measuring renal threshold phosphate concentration (TmP/GFR) [14]. Glomerular filtration rate (GFR) was determined by inulin clearance as previously described [12]. Osteocalcin in serum was determined by radioimmunoassay according to Price and Nishimoto [8] and urinary pyridinoline by high-performance liquid chromatography according to Black et al. [1]. Anthropometric measurements were performed according to international guidelines [2]. Reference data of normal children were obtained from the first Zurich Longitudinal Growth Study [7]. Skeletal X-rays of the left hand were performed at 6-monthly intervals, of knees and hips at 12-monthly intervals. Bone age was determined by the method of Tanner-Whitehouse (TW2, radio ulna score) [11]. Ultrasound imaging of the kidneys was performed at yearly intervals. Approval for the study was obtained from the local hospital ethical committee.

Results

In the year prior to start of rhGH treatment, height SDS for chronological age decreased slightly by 0.1 SD in patients 1 and 2 and remained stable in patient 3. RhGH treatment increased height velocity from 4.5 (3.0–4.7) cm/year to 8.5 (7.1–9.5) cm/year during the 1st treatment year and improved height SDS in all three patients (Table 1). The improvement in height SDS was most pronounced during the 1st treatment year and slowed down over the next 2 years. Sitting height SDS was normalized in two patients, whereas the increase in subischial leg length SDS was much lower (Table 1). The disproportion between sitting height and subischial leg length, which was already present at start of GH treatment, increased with time and was most marked after the 2nd and 3rd treatment years (Fig. 1). Improvement in height was accompanied by a significant

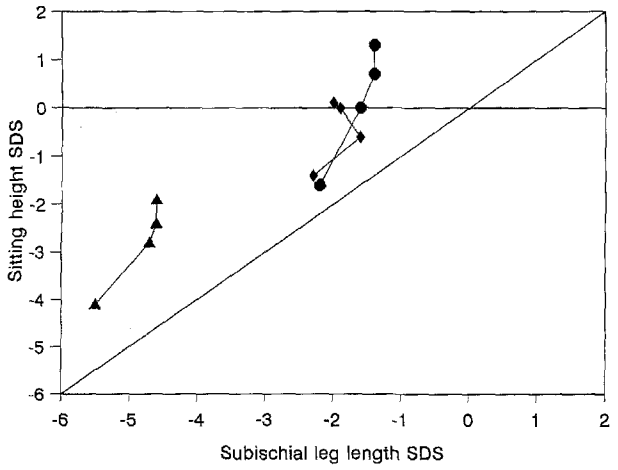

Fig.1 Segmental growth in three patients with hypophosphataemic rickets during 3 years of treatment with rhGH. The disproportion between sitting height and subischial leg length was already noted at start of rhGH treatment. It increased progressively during rhGH treatment. Patient 1 (▲), Patient 2 (●), Patient 3 (◆)

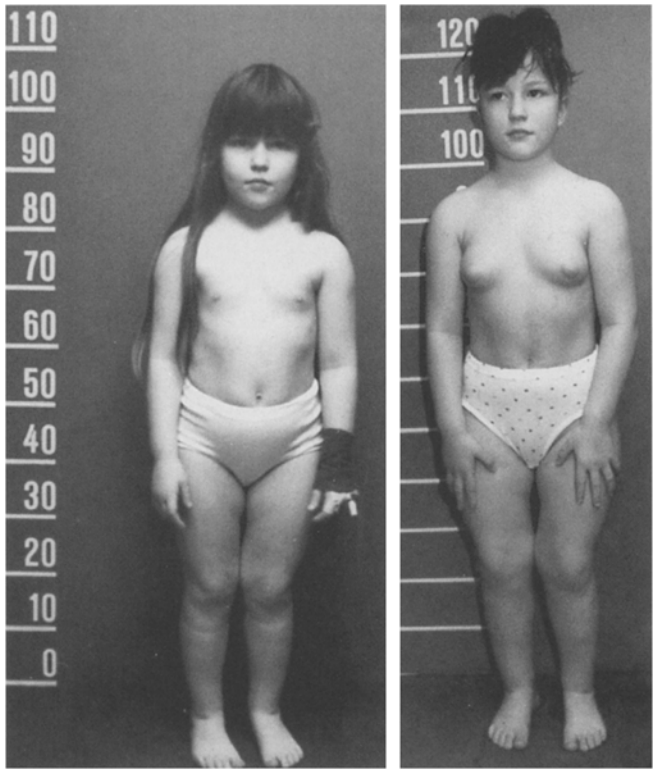

Fig.2 Clinical photographs of patient 1 taken at start of treatment with rhGH at the age of 8.8 years (*left*) and after 3 years of rhGH treatment (*right*). The ratio of trunk height to leg height was already increased at start of rhGH, and deteriorated after 3 years of rhGH treatment. No major bending of the lower limbs occurred during rhGH treatment

increase in serum insulin-like growth factor 1 and insulin-like growth factor binding protein 3 concentrations (Table 1). Bone age, which was slightly retarded at start of rhGH treatment, advanced between 4.5 and 6.0 years within the 3 years of rhGH treatment (Table 1).

The radiological signs of rickets, which were modest at start of rhGH treatment, worsened only in patient 1 during the 3rd treatment year. By photographic documentation no major bending of lower limbs was noted (Fig. 2). The effect of rhGH on bone was also documented by biochemical investigations: a slight increase in serum phosphate concentration occured for at least 12 months (Table 1); TmP/GFR was not normalized but increased slightly from 0.52 (0.43–0.58) mmol/l to 0.67 (0.51–0.69) mmol/l when measured after 3 months. This effect was reversible after discontinuation of rhGH treatment for 1 week, 12 months after the start of the study. Serum calcium concentrations remained unchanged during rhGH treatment. However, serum alkaline phosphatase levels increased in all three patients and serum intact parathyroid hormone concentration transiently rose above the upper normal limit of 6 pmol/l for at least 12 months in all three patients (Table 1). Urinary pyridinoline increased from 2.78 (2.53–3.31) mg/g creatinine at start to 3.79 (2.99–4.38) mg/g creatinine after 6 months of rhGH treatment, whereas no consistent change in serum osteocalcin concentrations was noted. Ultrasound imaging documented pre-existing low grade nephrocalcinosis in patients 2 and 3 which did not increase during the study period. GFR and urinary calcium excretion were not affected by rhGH (Table 1).

Discussion

The present study documents that the growth promoting effect of rhGH, reported previously in a 6-month short-term study [15], is sustained for at least 3 years; however, rhGH stimulated spinal growth to a greater extent than subischial leg growth. This effect increased with time in prepubertal and pubertal children (Fig. 1). Untreated XLH mainly affects the limb growth, which is responsible for the major part of statural growth in early childhood [9] and during puberty [10]. Since the present pilot study was uncontrolled, the question remains open whether rhGH treatment increases the ratio of trunk growth over leg growth compared to the natural course of segmental growth in this disease. It may be argued that puberty and the effects of sex steroid secretion may have confounded the results. However, the more pronounced response to rhGH of the spine as compared to the lower extremities was already observed during the 1st treatment year, when all three children were still prepubertal. Furthermore, during the pubertal growth spurt segmental growth of the extremities is more increased than spinal growth, resulting in a decrease of the ratio of sitting height over subischial leg length [10]. Therefore, the pubertal progress observed

during the 2nd and 3rd treatment year would, if anything, have weakened the disproportionate growth pattern attributable to rhGH treatment. The opposite was observed in all three patients.

It is of interest to note that also calcitriol treatment and oral phosphate supplementation do not stimulate limb growth [4]. It is not clear why the spine responds better to calcitriol and phosphate treatment as well as to rhGH than the limb bones.

Calcitriol and oral phosphate supplementation was kept constant during the year prior to rhGH and during the entire study period. The observed fall in urinary phosphate excretion may indicate decreasing treatment compliance. Although rhGH raised TmP/GFR slightly and serum phosphate concentrations increased during the 1st treatment year, we have the impression that the development of transient secondary hyperparathyroidism was not a direct consequence of rhGH, but correlated with periods of higher phosphate intake documented by urinary phosphate excretion.

Concern has been raised rhat rhGH may induce hypercalcuria during calcitriol treatment [6]. However, rhGH did not increase urinary calcium excretion and did not contribute to nephrocalcinosis. Furthermore, rhGH did not negatively influence GFR. The increase in serum concentration of alkaline phosphatase seems to be mainly an effect of increased growth velocity, as observed for rhGH treatment in other diseases [12].

Significant ricketic lesions developed in only one patient during the 3rd treatment year. We assume that rhGH did not have a major effect on the metabolic bone disease, although we cannot exclude that histological changes in the metaphyses and bowing of the lower limbs may have contributed in part to the reduced growth rate of the lower extremities.

After 3 years of rhGH, total body height, which was below the 3rd percentile in all three patients at start of rhGH treatment, increased to the 15th percentile in patient 2 and to the 50th percentile in patient 3. Nevertheless, it has to be taken into account that their final height may be below these percentiles, because all three patients entered puberty during the treatment period and a rapid bone age advancement was observed (Table 1). In addition, patient 2 had an early onset of puberty and a rapid advancement of pubertal signs. From our limited experience it cannot be conclusively decided whether rhGH influences puberty in XLH. However, our experience does not support the suspicion of Steendijk and Hauspie [9] that the pubertal onset is delayed in XLH.

In summary, our observations suggest that rhGH treatment of patients with XLH accelerates growth by improving sitting height more than leg length, thus worsening the pre-existing disproportion of these children.

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