Effects of Growth Hormone Treatment on Body Proportions and Final Height Among Small Children With X-Linked Hypophosphatemic Rickets

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ABSTRACT. Background. X-linked hypophosphatemic rickets (XLH) is characterized by rickets, disproportionate short stature, and impaired renal phosphate reabsorption and vitamin D metabolism. Despite oral phosphate and vitamin D treatment, most children with XLH demonstrate reduced adult height.

Objective. To determine the beneficial effects of recombinant human growth hormone (rhGH) therapy on body proportions and adult height among patients with XLH.

Methods. Three initially prepubertal short children (age, 9.4–12.9 years) with XLH were treated with rhGH for 3.1 to 6.3 years until adult height was attained.

Results. rhGH treatment led to sustained increases in standardized height for all children. The median adult height was 0.9 SD (range: 0.5–1.3 SD) greater than that at the initiation of rhGH treatment and exceeded the predicted adult height by 6.2 cm (range: 5.3–9.8 cm). However, longitudinal growth of the trunk was stimulated more than leg growth. During rhGH treatment, the standardized sitting height increased by 1.6 SD (range: 1.1–2.7 SD), compared with baseline values. In contrast, the median subischial leg length did not change consistently (median change: 0.3 SD; range: −0.1 to 0.6 SD).

Conclusion. The increase in final height after rhGH treatment is of potential benefit for children with XLH. However, the exaggeration of disproportionate truncal growth observed for our prepubertal patients is a potential negative effect of treatment and should be confirmed with additional studies. Pediatrics 2004;113:e593–e596. URL: http://www.pediatrics.org/cgi/content/full/113/6/e593; growth hormone treatment, hypophosphatemic rickets, growth failure, disproportionate growth, final height.

ABBREVIATIONS. XLH, X-linked hypophosphatemic rickets; GH, growth hormone; rhGH, recombinant human growth hormone.

X-linked hypophosphatemic rickets (XLH) is an inherited disorder of phosphate homeostasis characterized by disproportionate short stature, rickets and osteomalacia, hypophosphatemia, aberrant phosphate reabsorption, and disturbance of vitamin D metabolism.1 XLH is caused by mutations in the PHEX gene, encoding a membrane-bound endopeptidase. PHEX is expressed in bones and teeth but not in kidney, and efforts are underway to elucidate how PHEX function relates to the mutant phenotype.2

Pharmacologic treatment consists of oral phosphate supplementation and calcitriol administration. Although this therapy usually leads to an improvement of rickets, the effects on longitudinal growth are often disappointing.3 Despite adequate phosphate and calcitriol treatment, most previous studies reported reduced adult height among children with XLH.4–7 In addition, children with XLH present with disproportionate growth, ie, relatively preserved trunk growth but severely diminished leg growth.8 Previous studies demonstrated that treatment with recombinant human growth hormone (rhGH) was able to improve short- and long-term longitudinal growth among small children with XLH.9–15 However, we and others11,12 noted that short-term rhGH treatment could aggravate disproportionate growth among these children. Here we report the effects of long-term rhGH treatment on longitudinal growth and body proportions among 3 initially prepubertal, short children with XLH who were prospectively monitored after the initiation of rhGH treatment, until their final heights were achieved.

PATIENTS AND METHODS

Three short prepubertal children with XLH, with ages of 12.9 years (patient 1), 9.4 years (patient 2), and 11.1 years (patient 3), began to receive rhGH treatment. Patient 1 was female, and patients 2 and 3 were male siblings. At the time of diagnosis, all patients fulfilled the clinical, biochemical, and radiologic criteria for diagnosis of the disease.1 In each case, X-linked dominant inheritance was confirmed by analysis of the pedigrees. The children had been treated with calcitriol and phosphate supplements for at least 5 years. They had prescriptions of fixed individual doses of calcitriol (1–1.5 μg/day) and oral phosphate supplementation (0.8–2.1 g/day) during the year before rhGH treatment. The individual prescriptions were not changed during the study period. Growth hormone (GH) deficiency was excluded with GH stimulation tests with L-arginine (peak serum GH concentration of >10 μg/L) and normal night serum GH concentration profiles (>2 peaks of >10 μg/L). rhGH (0.33 mg/kg per week) was administered daily, in the evening, as subcutaneous injections.

Anthropometric measurements were performed at 3-month intervals, with standard techniques.16 For calculations of age- and gender-related SD scores, the first Zurich longitudinal study was used as a reference.17 SD values for sitting height and subischial leg length were used to evaluate disproportionate growth. Bone age was assessed at yearly intervals with the method described by Greulich and Pyle.18 Pubertal stage was assessed according to the method described by Tanner.19 Predicted adult height was calculated from the patient’s height and bone age by the method described by Bayley and Pinneau.20 Final (adult) height was de-
fined as epiphysial closure on hand radiographs and/or a height increase of <1 cm/year in the preceding year. The laboratory methods used were described elsewhere. Ultrasonographic imaging of the kidneys was performed at yearly intervals. The study protocol was approved by the ethics committee of the University of Heidelberg, and written informed consent was obtained from the parents, with assent by the patients.

RESULTS

For each of the 3 patients, rhGH treatment led to a sustained increase in standardized height (Fig. 1). The median adult height was 0.9 SD (range: 0.5–1.3 SD) greater than that at the initiation of rhGH treatment, exceeded the predicted adult height by 6.2 cm (range: 5.3–9.8 cm), and was close to the genetic target height for 2 of the 3 patients (median difference: −3.8 cm; range: −13.4 to 0.1 cm) (Table 1). At baseline, trunk growth was more preserved than leg growth. During rhGH treatment, the standardized sitting height continuously increased for all patients (Fig. 1). At the final height, the median sitting height was increased by 1.6 SD (range: 1.1–2.7 SD), compared with baseline values. In contrast, the median subischial leg length did not change consistently (median change: 0.3 SD; range: −0.1 to 0.6 SD). During rhGH treatment, there was no obvious change in the degree of bowing of the legs. The median distance between the medial condylars of the tibia was 5.8 cm (range: 4.3–7.6 cm) at baseline and was 6.3 cm (range: 5.2–8.7 cm) at the final height.

During the first 6 months of rhGH treatment, a transient increase in the renal tubular maximal reabsorption of phosphate, relative to the glomerular filtration rate, from 0.53 mmol/L (range: 0.43–0.58 mmol/L) to 0.67 mmol/L (range: 0.52–0.69 mmol/L) and a concomitant increase in serum phosphate levels from 0.7 mmol/L (range: 0.5–0.8 mmol/L) to 0.9 mmol/L (range: 0.7–1.1 mmol/L) were noted. In addition, serum intact parathyroid hormone concentrations transiently increased above the upper normal limit of 6 pmol/L. During rhGH treatment, there were no changes in creatinine clearance, urinary calcium and phosphate excretion, serum glucose levels, or the degree of nephrocalcinosis on renal ultrasonograms, which was noted for 2 of 3 patients at baseline (data not shown).

DISCUSSION

Our study provides evidence that rhGH treatment improves longitudinal growth and final height among small prepubertal children with XLH. Before the initiation of rhGH treatment, the children presented with body disproportion, ie, short legs and relatively preserved trunk growth. For all children, rhGH therapy predominantly stimulated trunk growth, whereas leg growth was stimulated less, thereby increasing the preexisting body disproportion.

Despite early positive reports of short-term studies, previous long-term studies of children with XLH could not demonstrate sustained catch-up growth during calcitriol and phosphate treatment. In the present study, vitamin D and phosphate administration was not changed during the observation period. In addition, metabolic control with respect to serum levels of phosphate, parathyroid hormone, and alkaline phosphatase did not change with time. However, the final height was 5 to 10 cm greater than the predicted adult height for our patients. It has been demonstrated that height prediction for children with XLH is quite accurate and might actually overestimate adult height for these children. Therefore, we assume that rhGH treatment increased the adult height for our patients. However, crucial methodologic factors in this study were the small number of patients and the lack of a control group.

Several clinical trials (mostly uncontrolled) on the effect of rhGH treatment on longitudinal growth

| TABLE 1. Anthropometric Characteristics of rhGH-Treated Children with XLH |
|---------------------|---------------------|---------------------|
| Gender              | Age at baseline* (y) | Bone age at baseline* (y) |
| Female              | 12.9                | 11.4                |
| Male                | 12.9                | 11.1                |
| Age at baseline* (y) | 12.9                | 11.4                |
| Bone age at baseline* (y) | 9.4                | 9.0                |
| Height at baseline* (SD) | −2.1               | −2.0               |
| Subischial leg length at baseline* (SD) | −2.3               | −2.2               |
| Sitting height at baseline* (SD) | −1.5               | −1.6               |
| Genetic target height (cm) | 170.5              | 166.8              |
| Genetic target height (SD) | 1.0                | −1.6               |
| Predicted adult height at baseline* (cm) | 147.3              | 156.8              |
| Predicted adult height at baseline* (SD) | −2.9               | −3.1               |
| Duration of rhGH treatment (y) | 3.1                | 5.6                |
| Age at adult height (y) | 16.0                | 15.0               |
| Adult height (cm) | 157.1              | 163.0              |
| Adult height (SD) | 1.3                | 166.9              |
| Adult height (SD) | 1.0                | −0.7               |
| Subischial leg length at adult height (SD) | −1.7               | −2.3               |
| Sitting height at adult height (SD) | 0.1                | 1.1                |
| Sitting height at adult height (SD) | 0.7                | 0.3                |

among short children with XLH have been reported.9–15 The patients were treated for periods of 0.5 to 9 years, with rhGH doses of 0.15 to 0.56 mg/kg per week. The median increase in standardized height amounted to 1.2 SD (range: 0.7–1.4). Baroncelli et al15 recently reported final height data for 6 children with XLH who were treated with rhGH for up to 9 years. Whereas the mean standardized height increased by 1.0 SD at the final height for the rhGH-treated children, the standardized height did not change significantly in the control group.

It is unclear whether rhGH therapy affects the onset or duration of the pubertal growth spurt among children with XLH. Among children with XLH without rhGH treatment, a pubertal growth spurt of normal magnitude has been observed.5 In a previous study of rhGH treatment of children with XLH, longitudinal growth was stimulated mainly during the prepubertal growth period, whereas the standardized height during the pubertal growth period even decreased.15 In accordance with this finding, 2 of our patients demonstrated a slight decrease in standardized height after 3 years of rhGH treatment during the pubertal growth period. These observations suggest that the expected increase in final height during the prepubertal growth period might be counterbalanced partly by decreased pubertal growth.

Why patients with XLH demonstrate disproportionate growth is not fully understood. Various skeletal abnormalities have been demonstrated in an animal model of XLH, ie, Hyp mice.21,22 In addition to rickets and osteomalacia, Hyp mice exhibit craniosynostosis because of premature fusion of the coronal suture and abnormal skull morphology, with deficient linear growth of the nasal bone. It has been assumed that the abnormal bone formation in Hyp mice is determined not only by hypophosphatemia but also by an intrinsic osteoblast defect in the mutant strain.23 In view of an underlying osteoblast defect among patients with XLH, the predominant involvement of the lower limbs, compared with lesser involvement of the spine, might be attributable partly to the greater mechanical stress of the legs, compared with the spine, and/or to a differential pattern of organ-specific activation of PHEX within the skeleton.24

Phosphate and vitamin D treatment fails to normalize body proportions among children with XLH.8 In vitro studies showed that bone formation in bone cells from Hyp mice was only partly normalized with high-dose 1,25-dihydroxy-vitamin D3 treatment.25 In the present study, rhGH treatment preferentially stimulated trunk growth rather than leg growth, thereby aggravating the preexisting body disproportion. This was not explained by increased bowing of the legs.11 Body proportions have been measured in only 3 previous studies of children with XLH treated with rhGH.11,12,15 In accordance with our study, Reusz et al12 reported an increase in body disproportion among children treated with rhGH for 1 year. In contrast, Baroncelli et al15 did not observe changes in body proportions for 6 children treated with rhGH until final height. It is important to note that the patients reported in those studies differed significantly with respect to the degree of stunting at the initiation of rhGH therapy. The median standardized height at baseline was −2.0 SD in the present study and was −3.4 SD in the Italian study, which used the old reference values of Tanner,19 thereby underestimating the degree of stunting by at least 0.5 SD, compared with more recent standards.17 Therefore, the conflicting results might be influenced partly by differences in stunting, ie, severity of the disease.

Recent studies indicate that in various forms of short stature, eg, uremic growth failure, longitudinal growth of the lower limbs is generally more affected than trunk growth, leading to body disproportion.25 It has been speculated that this is attributable to the vital need of the body to maintain the function of the internal organs within the trunk. rhGH therapy among short children with chronic renal failure has been shown to improve body disproportion.25 The finding that this is not the case for patients with XLH suggests that, in this particular disease, the underlying osteoblast defect might be more evident in the long bones of the legs than in the vertebræ.

When these findings are taken together, it is tempting to speculate that the growth-stimulating properties of rhGH only partly overcome the underlying osteoblast defect in XLH, thereby preferentially stimulating the less diseased part of the skeleton. Unfortunately, data on the effect of rhGH on bone formation in Hyp mice are lacking.

It has been speculated that the growth-stimulating effect of rhGH in XLH might be attributable to increased renal phosphate reabsorption, promoting bone formation. In accordance with this hypothesis, Baroncelli et al15 reported a sustained increase in the renal phosphate threshold concentration during rhGH treatment. However, we and others7,12 did not observe consistent effects of rhGH treatment on renal phosphate reabsorption. In addition, the finding of Roy et al26 that rhGH treatment failed to stimulate renal phosphate reabsorption in Hyp mice argues against a major effect of rhGH treatment on the phosphorous threshold in XLH.

CONCLUSIONS

Treatment with rhGH might have potential positive effects on final height and thus psychosocial rehabilitation among short patients with XLH. However, the aggravation of disproportion observed for our patients must be viewed critically. Randomized, clinical trials are needed to clarify the effects of rhGH on segmental growth among patients with XLH.

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