Growth hormone treatment improves final height in children with X-linked hypophosphatemia

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Abstract

Background/aim: Despite optimal conventional treatment (oral phosphate supplements and active vitamin D analogs), about 40–50% of children with well-controlled X-linked hypophosphatemia (XLH) show linear growth failure, making them less likely to achieve an acceptable final height. Here, we studied the hypothesis that rhGH treatment improves final height in children with XLH and growth failure.

Methods: Two cohorts of children with XLH were included in this retrospective longitudinal analysis: (1) a cohort treated with rhGH for short stature (n = 34) and (2) a cohort not treated with rhGH (n = 29). The mean duration of rhGH treatment was 4.4 ± 2.9 years. We collected the auxological parameters at various time points during follow-up until final height.

Results: In rhGH-treated children, 2 years of rhGH therapy was associated with a significant increase in height from −2.4 ± 0.9 to −1.5 ± 0.7 SDS (p < 0.001). Their mean height at rhGH discontinuation was −1.2 ± 0.9 SDS and at final height was −1.3 ± 0.9 SDS corresponding to 165.5 ± 6.4 cm in boys and 155.5 ± 6.3 cm in girls. Notably, the two groups had similar final heights; i.e., the final height in children not treated with rhGH being −1.2 ± 1.1 SDS (165.4 ± 6.8 cm in boys and 153.7 ± 7.8 cm in girls), p = 0.7.

Conclusion: Treatment with rhGH permits to improve final height in children with XLH and growth failure, despite optimal conventional treatment. We propose therefore that rhGH therapy could be considered as an option for short stature in the context of XLH.

Keywords: X-linked hypophosphatemia, Rickets, Fibroblast growth factor 23, Recombinant human growth hormone, Final height

Introduction

X-linked hypophosphatemia (XLH) is the most common form of hereditary rickets with an incidence of 3.9–5 per 100,000 live births [1]. It is a genetic disease caused by loss of function mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) gene, localized on Xp22.1. PHEX encodes an endopeptidase highly expressed in bone (osteoblasts, osteocytes) and tooth (odontoblasts) cells [2]. Animal studies indicate that loss of PHEX function...
results in enhanced secretion of the phosphaturic hormone fibroblast growth factor 23 (FGF23), which leads to renal phosphate wasting, hypophosphatemia and insufficient calcitriol (1,25(OH)₂D) synthesis [3, 4]. Chronic hypophosphatemia and low levels of 1,25(OH)₂D lead to mineralization failure which, in children with XLH, manifests clinically as rickets, e.g., severe skeletal deformities and short stature, recurrent dental abscesses and craniosynostosis. Poor growth and disproportionate short stature are often the first symptoms of XLH in children. In children with XLH, length at birth is reported as normal [1] but growth retardation becomes notable during the first years of life [5, 6], resulting in a mean height in these patients 2 standard deviation scores (SDS) below the mean height of the reference population [7, 8]. Despite adequate conventional treatment (phosphate supplemen-
tations and active vitamin D analogs), even when started early in life, the growth retardation may persist. Indeed, most studies have reported that about half of treated patients still have short stature at the end of growth (<−2 SDS) [9–11] which results in reduced final adult height [5, 7, 9, 12–14].

Background
Treatment with recombinant human growth hormone (rhGH) has been recently proposed as a support to improve linear growth in children with XLH showing growth failure regardless of well controlled disease. It is known that GH exerts its effect on growth cartilage through the action of insulin-like growth factor-1 (IGF-1), which plays an important role in the differentiation and maturation of chondrocytes of the growth plate. IGF-1 also stimulates osteoblastogenesis and enhances collagen secretion and bone matrix mineralization. In osteocytes, IGF-1 helps in transducing mechanical stimuli and promoting the anabolic response. Additionally, the IGF system interacts with other hormones, such as parathyroid hormone and sex steroids, promoting bone anabolism [15]. Moreover, it is thought that GH, directly and indirectly through IGF-1, may increase renal phosphate reabsorption and thereby serum phosphate levels [16–19]. Indeed, receptors for GH and IGF-1 have been identified in the proximal renal tubule. In line with this, it has been shown that the positive effect of rhGH administration on phosphate metabolism is likely related to the stimulation of renal phosphate reabsorption and 1α-hydroxylase activity [20–22]. It is interesting to note that patients with XLH may have a transient increase in serum phosphate during rhGH treatment attributable to a transient decrease in urinary phosphate excretion [16]. In support of these facts, several clinical studies have demonstrated beneficial effect of rhGH on growth, especially if started at a prepubertal age [16, 17, 20–24], and importantly, no side effects have been reported during rhGH treatment. On the other hand, only one study [25] has explored whether the height is maintained after rhGH withdrawal, and especially, whether rhGH treatment improves final height in XLH.

Proposal of the current study is to demonstrate the effect of rhGH on final height in children with XLH and poor growth.

Results
The whole cohort of children with XLH
The characteristics of the cohort included in the present study are summarized in Table 1. We selected 63 children with XLH (23 boys and 40 girls) among which 56 (89%) carried the PHEX mutation. Thirty-four of these children received treatment with rhGH for persistent short stature despite adequate conventional treatment; the other 29 were not given rhGH because of adequate growth or because they decided not to take this additional therapy and to continue conventional treatment. Comparing the two groups, we did not find any differences in the distribution of boys and girls, the rate of PHEX mutations, age at XLH diagnosis or duration of conventional treatment. Interestingly, rhGH-treated children tended to have lower birth weight and length, than those not treated with rhGH, but this difference did not reach statistical significance.

Final height under rhGH treatment
Thirty-four patients treated with rhGH started treatment at a mean age of 9.8 ± 3.5 years and continued it for 4.4 ± 2.9 years. The changes in height SDS from diagnosis to final height are shown in Table 2 and Fig. 1. As expected [10], rhGH-treated children had significantly shorter stature at XLH diagnosis (−2.2 ± 1.2 SDS) than those who did not receive rhGH (−0.8 ± 1.6 SDS, p < 0.001). In the former group of children height did not improve, remaining at −2.4 ± 0.9 SDS after almost 7 years of conventional treatment. Having started rhGH at a mean age of 9.8 ± 3.5 years, their height SDS was significantly higher than baseline after 2 years of treatment, at the end of rhGH treatment and at final height (−1.5 ± 0.7, p = 0.003, −1.2 ± 0.9, p < 0.001 and −1.3 ± 0.9 SDS, p < 0.001 respectively). Notably, the height SDS gain was maintained until final height despite the discontinuation of rhGH. The total height gain was 1.2 ± 0.9 SDS. Out of these 34 children treated with rhGH, 75% reached a final height > −2 SDS. Importantly, the final height in children of this cohort was not significantly different from children in the cohort of children who did not receive rhGH (−1.3 ± 0.9 vs. −1.2 ± 1.1 SDS, p = 0.7).
Interestingly, the rate of rhGH treatment was somewhat higher in children with a de novo diagnosis of XLH (without a family history of XLH) than those with a family history, though the difference did not reach significance (64.3% vs. 43.3%, \( p = 0.091 \)).

Subgroup analysis of children treated with rhGH + aGnRH
As mentioned in the methods, a small group of children (\( n = 17; 27\% \)) with clinical signs of early puberty was

### Table 1 Characteristics of children with X-linked hypophosphatemia included in the study

| Parameters                        | Patients treated with rhGH | Patients not treated with rhGH | \( p \) |
|-----------------------------------|-----------------------------|-------------------------------|--------|
| Number of patients                | 34                          | 29                            | –      |
| Boys/girls, n (%)                 | 13 (38%)/21 (62%)           | 10 (34%)/19 (66%)             | 0.49   |
| Birth weight, SDS                 | \(-0.5 \pm 2.0\)            | \(0.4 \pm 1.2\)               | 0.11   |
| Birth length, SDS                 | \(-0.5 \pm 1.9\)            | \(0.5 \pm 1.2\)               | 0.09   |
| Patients carrying a PHEX mutation | \(n = 32\) (94%)            | \(n = 24\) (86%)              | 0.29   |
| Age at XLH diagnosis, years       | \(3.4 \pm 3.4\)             | \(2.6 \pm 2.6\)               | 0.32   |
| Duration of conventional therapy, years | \(12.6 \pm 4.9\)       | \(14.0 \pm 3.0\)             | 0.20   |
| Age at menarche, years            | \(13.4 \pm 1.3\)            | \(12.8 \pm 0.8\)             | 0.15   |
| Age at rhGH start, years          | \(9.8 \pm 3.4\)             | –                            | –      |
| Duration of rhGH treatment, years | \(4.4 \pm 2.9\)             | –                            | –      |
| Dose of rhGH (µg/kg/day)          | \(77.4 \pm 14.5\)           | –                            | –      |
| – at the beginning of treatment   | \(77.4 \pm 14.5\)           | –                            | –      |
| – at the end of treatment         | \(66.8 \pm 20.5\)           | –                            | –      |
| Patients treated with a GnRH, n (%) | \(15 (47\%)\)            | \(2 (7\%)\)                 | < 0.001|

**rhGH**: Recombinant human growth hormone; aGnRH: gonadotropin-releasing hormone analog; SDS: standard deviation score or Z-score

### Table 2 Changes in height SDS of children with X-linked hypophosphatemia followed-up until final height

| Time points of follow-up | Patients treated with rhGH (\( n = 34 \)) | Patients non treated with rhGH (\( n = 29 \)) |
|--------------------------|-------------------------------------------|-----------------------------------------------|
|                          | Age, years | Height SDS | Age, years | Height SDS |
|                          | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| Birth                    | –          | \(-0.5 \pm 1.9\) | –          | \(0.5 \pm 1.2\) |
| Diagnosis                | 3.5 ± 3.4  | \(-2.2 \pm 1.2\) | 2.6 ± 2.6  | \(-0.8 \pm 1.6\) |
| Start of rhGH            | 9.8 ± 3.5  | \(-2.4 \pm 0.9\) | 9.8 ± 0.0  | \(-0.7 \pm 0.9\) |
| After 2 years of rhGH    | 11.8 ± 3.4 | \(-1.4 \pm 0.7\) | 11.9 ± 0.0 | \(-0.9 \pm 0.9\) |
| At the end of rhGH       | 14.2 ± 3.1 | \(-1.2 \pm 0.9\) | 14.2 ± 0.0 | \(-1.1 \pm 1.1\) |
| Final height             | 18.3 ± 3.2 | \(-1.3 \pm 0.9\) | 16.9 ± 2.1 | \(-1.2 \pm 1.1\) |

165.5 ± 6.4 cm in boys
155.5 ± 6.3 cm in girls

Height gain at the end of rhGH | 1.2 ± 0.7 | – |
Height gain at final height    | 1.2 ± 0.9 | – |

**rhGH**: Recombinant human growth hormone; SDS: standard deviation score or Z-score
and growth velocity in children with XLH [24]. This present study is the first to describe and consolidate the notion that rhGH has a positive effect on final height in XLH children with short stature. Indeed, we demonstrate that the treatment with rhGH is associated with an increase in final height in children who still manifested short stature despite optimal conventional treatment. The height gain obtained was most significant during the first 2 years of treatment and the gain was sustained until the achievement of final height, despite the rhGH discontinuation. Most importantly, treatment with rhGH allows these children to achieve an acceptable final height comparable to that of children who did not receive rhGH (165.5 ± 6.4 cm in boys and 155.5 ± 6.3 cm in girls). At final height, of the whole cohort of 63 patients, 79.5% reached a height > −2 SDS (75% in the cohort treated with rhGH and 83.3% in the cohort not treated with rhGH).

The effect of XLH on growth is independent of disorders of growth hormone (GH) secretion/action or nutritional deficiencies [26], and only few patients with XLH have a GH deficit [5, 27]. Impaired bone elongation in XLH resides at least partly in structural abnormalities of the growth plate, as it was described in a murine model of XLH (Hyp mice) by Fuente et al., which hinder normal endochondral ossification [28]. These abnormalities are, first of all, due to hypophosphatemia which attenuates chondrocyte differentiation and hypertrophic chondrocyte apoptosis leading to an increase in the hypertrophic layer of the growth plate [29]. Secondly, FGF23 inhibits chondrocyte differentiation and might also have a causal role in growth retardation in XLH [30, 31]. The latter could probably explain the failure to achieve acceptable growth using conventional treatment with phosphate supplementation and active vitamin D analogs.

Currently, there are no widely accepted guidelines for the prescribing of rhGH to treat short stature in XLH children. Nonetheless, the recent clinical recommendations on the diagnosis and management of XLH [4] state that rhGH may be considered for children with XLH who present short stature despite well-controlled disease (normal levels of alkaline phosphatase and parathyroid hormone). In our study, the indications for rhGH treatment were height ≤ −2 SDS despite well-controlled rickets on conventional treatment at least for 1 year and a height prognosis ≤ −2.5 SDS.

Another open question regarding rhGH treatment is how long it should be given. In the majority of studies, the duration of rhGH treatment varies from 1 to 6 years [16, 19, 22, 27, 32–34]. Nonetheless, we observed that the acceleration of growth takes place during the first 2 years of treatment without any further significant improvement in height afterwards. Following the discontinuation...
of rhGH, height SDS remained stable until final height was reached. Therefore, it could be hypothesized that the duration of rhGH treatment could be limited to 2 years, given the constraints of the treatment (daily subcutaneous injections). On the other hand, it has been well demonstrated that it is important to give rhGH treatment throughout the whole period of accelerated growth to maintain the benefit of this treatment on height through the direct action on the growth plate [35].

The doses of rhGH treatment in our study were relatively high, averaging 77 µg/kg/day at initiation and 67 µg/kg/day at discontinuation. This contrasts with other previous research in which the average dose of rhGH was about 30 µg/kg/day, though these researchers failed to show a beneficial impact of rhGH on growth acceleration [36]. This suggests that higher doses of rhGH may be needed to promote growth in XLH. If such treatment is given, rhGH doses should be adjusted every 3–4 months to keep IGF-1 blood levels below 2 SDS [37, 38].

Finally, almost half of children treated with rhGH had also been treated with aGnRH, a treatment blocking puberty, thus influencing final height. We found no significant differences in final height between the subgroups of children who were and were not treated with aGnRH in addition to rhGH. By performing this subgroup analysis, we ruled out potential bias from the possibility that the positive effect of rhGH treatment on final height could depend on aGnRH treatment.

We recognize that the present study is retrospective with all the limitations that this entails. On the other hand, its strengths include the longitudinal design and the fact that it was performed in a large cohort of children with a disease as rare as XLH.

In conclusion, we believe that, to achieve an acceptable final height, rhGH may be an appropriate option for children with XLH who still have short stature despite well-controlled disease. We would thus recommend implementing rhGH treatment in the therapeutic management of XLH for children who do not grow correctly. Though the availability of novel therapeutic strategies for XLH, namely anti-FGF23 antibodies, has recently changed XLH landscape, the results of this study may help prescribing a more individualized treatment as the disease manifestations are very variable between patients even in affected siblings.

Material and methods

Patients

The present retrospective longitudinal observational study was conducted in the Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, Filière OSCAR and Platform of expertise for rare diseases Paris Saclay, Bicêtre Paris Saclay Hospital, France. The diagnosis of XLH was based on clinical and/or radiological evidence of rickets, biochemical evidence of phosphate wasting associated with elevated levels of FGF23 and/or a variant in the PHEX gene. As soon as a child was diagnosed with XLH, we proceeded with a clinical examination of parents which involves a detailed clinical history focused on possible XLH manifestations during childhood such as leg deformities, recurrent dental abscesses, poor growth, short stature, and pain; measurement of serum phosphate levels; and genetic analysis for the mutations in PHEX, DMP1, FGF23, ENPP1, FAM20C, FGFR1, KLOTHO genes. In the absence of clinical and biochemical signs of hypophosphatemia, a subject was considered as non-affected with XLH. After diagnosis, all children started treatment with active vitamin D analogs (alfacalcidol) and phosphate supplements according to international recommendations [4].

In the present study, we included children with XLH who (i) were born between 1988 and 2006; (ii) regularly visited in our hospital, and therefore, had a detailed growth chart available; and (iii) had reached their final height. The whole cohort included children with XLH who were treated with rhGH and also those who did not need rhGH treatment (serving as “control group”). Children who underwent lower limb surgery were excluded from the analysis.

The study was approved by the French National Data Processing and Liberties Commission (CNIL number 1920371v0), and in accordance with the Jardé law in France, the need for written consent was waived. After patients and/or their parents had been informed orally about the study, oral consent was obtained from parents and oral assent from minors (as appropriate). It was clarified that they had the right to withdraw from the study at any time by completing a form available through http://recherche.aphp.fr/eds/droit-opposition.

Treatments

Treatment with rhGH was given to children who (i) had a height ≤ −2 SDS, (ii) had received at least 1 year of adequate conventional therapy, and (iii) had a height prognosis ≤ −2.5 SDS. A thorough investigation was performed to exclude other causes of short stature. Some patients treated with rhGH were included in the prospective study promoted by INSERM and have been reported in Rothenbuhler and al. [24]. In all cases, rhGH was given as a subcutaneous injection 6 days a week; mean doses of rhGH at the beginning and withdrawal were 77.4 ± 14.5 and 66.8 ± 20.5 µg/kg/day, respectively. All children were compliant to the rhGH treatment.

A small group of children in both groups exposed or not to rhGH treatment who presented clinical signs of
early puberty received a GnRH (leuprorelin, sustained-release formulation at a dose of 11.25 mg every 3 months) to block early puberty. The decision to add the aGnRH treatment was normally made by the pediatric endocrinology team after careful evaluation. Patients and their families were informed and gave their consent to this therapy.

**Study protocol and methods**

The follow-up period was from disease diagnosis until the last visit. For each patient, we gathered data on parameters such as gestational age at birth, weight, length/height and body mass index (BMI) at several time points. For children treated with rhGH, we retrieved data at birth, at the time of XLH diagnosis, at the start of rhGH treatment, after 2 years of rhGH treatment, at the end of rhGH treatment and at the last visit, i.e., at final height. For children who did not receive rhGH treatment (the “control”), we collected the same types of data at equivalent stages during follow-up, namely, at birth, at the time of XLH diagnosis, at the ages at which patients in the other group initiated rhGH, 2 years later and at which they discontinued the treatment (i.e., mean ages of 9.8, 11.9 and 14.2 years, respectively) and at the last visit.

BMI was calculated using the formula weight (kg)/height (m)^2. Z-scores (SDS) for length/height, weight, and BMI were derived from the World Health Organization growth charts [39]. Z-scores for weight were calculated only for children between 0 and 10 years of age. Final height was defined as height achieved at the completion of growth, i.e., when bone age > 16 years and/or growth velocity < 2 cm/year [40, 41].

**Statistical analysis**

Statistical analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The results were expressed as mean±SD for continuous variables and as absolute number (percentage) for categorical variables. The comparisons of continuous variables were performed using Student’s t test or the Mann–Whitney U test or using one-way analysis of variance, as appropriate. All p values <0.05 were considered significant. Figures were plotted using the Prism Graph Pad software version 8.4.1.

**Abbreviations**

XLH: X-linked hypophosphatemia; PHEX: Phosphate-regulating gene with homologies to endopeptidases on the X chromosome; FGF23: Fibroblast growth factor 23; SDS: Standard deviation score; rhGH: Recombinant human growth hormone; aGnRH: Analog of gonadotropin releasing hormone.
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