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ORIGINAL ARTICLE

Somatropin and final height in Mexican paediatric population with growth hormone deficiency

Somatropina y talla final en población pediátrica mexicana con deficiencia de hormona de crecimiento

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What do we know about the subject matter of this study?

Treatment with somatropin increases linear growth and is effective in improving the final height in children with isolated growth hormone deficiency (IGHD). There is scarce available information on these results in the Latino population.

What does this study contribute to what is already known?

In Mexican children with IGHD, somatropin allows for normalizing the growth velocity and reaching the final height within the genetic potential. Final height is associated with the genetic potential height and somatropin dose.

Abstract

Treatment with recombinant growth hormone, or somatropin, increases linear growth and is effective in improving final height in children with isolated growth hormone deficiency (IGHD), however, the available information of these results in the Latin population is scarce. **Objective:** To evaluate the effect of somatropin on growth velocity and final height in Mexican children with IGHD, as well as to determine the factors associated with final height. **Patients and Method:** A retrospective study was conducted in 50 children with isolated and severe growth hormone deficiency treated with somatropin. Auxological characteristics were assessed before somatropin and at final height. Only patients with severe GH deficiency, with a peak GH value < 5 µg/L, were included. **Results:** 40% (n = 20) were girls. The basal height Z-score was -2.6 ± 0.4 vs final height Z-score 1.6 ± 0.7, with a Z-score of height increase of 1 ± 0.6. Ninety-two percent (n = 46) reached their genetic potential; somatropin dose was 33

Keywords:
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± 0.5 µg/kg/d, with a treatment duration of 4.16 ± 1.5 years. The highest growth velocity was observed during the first year. In the multivariate analysis, the association between final height, mid-parental target height (r = 0.30; p = 0.03, β = 0.7; p = 0.001), and somatropin dose (r = 0.63; p = 0.001, β = 0.30; p = 0.028) was observed. **Conclusions:** Somatropin treatment allows normalization of linear growth and the achievement of genetic height potential in most Mexican children with IGHD. Final height is associated with mid-parental height and somatropin dose, highlighting the importance of genetic potential and the dose-response effect of somatropin in establishing height prognosis.

Introduction

In pediatrics, short stature is one of the main reasons for consultation, in addition to being one of the most frequent pathologies in pediatric endocrinology. Short stature can be a normal variant (familial short stature and constitutional delay of growth and development) or be related to primary or secondary growth disorders. Growth hormone (GH) deficiency is a rare cause of short stature, with an estimated prevalence of 1:4000 children[1]. The diagnosis of GH deficiency in childhood requires the combination of clinical, auxological, biochemical (evaluation of the hypothalamic-pituitary GH-IGF-1 axis), and radiological aspects.

GH deficiency can be isolated or coexist with panhypopituitarism[2]. Isolated growth hormone deficiency (IGHD) is the most common pituitary hormone deficiency caused by congenital aspects or acquired; however, most are idiopathic. Mutations have been described in the growth hormone gene (*GH1*) or the GH-releasing hormone receptor (*GHRHR*) or other genes such as *BTK*, *RNPC3*, *GHSR*, and *SOX3*[3,4]. Different studies have shown that treatment with recombinant human GH, also known as somatropin, is effective in achieving an adequate final height, however, there is little information on these results in the Latin population with IGHD.

The objective of our study was to evaluate the effect of somatropin on growth velocity and final height in Mexican children with IGHD, as well as to determine the factors associated with final height.

Patients and Method

Retrospective study in children with severe GH deficiency treated with somatropin, seen between 2000 and 2019 in the pediatric endocrinology department of the Pediatric Hospital *Centro Médico Nacional Siglo SXXI* (CMN SXXI), from the public health system, in Mexico City. The CMN SXXI provides tertiary medical care to more than 5.5 million children in the southern zone of Mexico City, Guerrero, Oaxaca, Chiapas, Tabasco, Veracruz, and Tlaxcala[5].

The data were collected by reviewing the electronic medical record of each participant. School patients with GH deficiency were included, with auxological diagnosis defined as 1) height below 2 standard deviations (SD) from the mean; 2) height below 1.5 SD from the genetic potential height (GPH); 3) height below 2 SD from the mean and growth velocity (GV) over 1 year below the 25th percentile or a decrease below the 10th percentile for 6 months from chronological age in children older than 2 years and with bone age delayed by at least 2 SD from that expected for their chronological age.

GH deficiency was diagnosed according to international recommendations, using the auxological criteria previously mentioned, along with biochemical and radiological criteria[2]. The biochemical criteria included: 1) values below 2 SD of insulin-like growth factor 1 (IGF-I) and 2) a GH peak below 10 µg/L in the GH stimulation test through the insulin tolerance test. In this study, only patients with severe GH deficiency, defined by a GH peak value below 5 µg/L following the insulin tolerance test, were included.

IGHD was defined as the presence of isolated GH deficiency without other pituitary deficiencies[6]. Exclusion criteria included children with structural alteration in the hypothalamic-pituitary region, history of cranial radiation, severe cranioencephalic trauma, presence of neuroinfection, infiltrative or neoplastic diseases, children small for gestational age, children with dysmorphic syndromes, chromosomopathies, skeletal dysplasia, systemic or chronic diseases, malnutrition, overweight, obesity, precocious puberty, partial GH deficiency (GH peak between 5 and 10 µg/L after the insulin tolerance test), children who did not attend follow-up visits, patients with inadequate therapeutic adherence (therapeutic adherence < 85%) or who developed adverse drug reactions (hyperglycemia, hypersensitivity, myositis, intracranial hypertension).

The percentage of therapeutic adherence was calculated with the formula: (days of prescribed dose administered/days prescribed) ×100. More sensitive and specific methods to assess therapeutic adherence (e.g., digital devices) were not available.

Baseline characteristics included chronological age,

bone age (according to the Greulich-Pyle method), height (cm) (Harpenden stadiometer), height Z-score, GPH calculated as (mother's height + father's height) /2 ± 6.5 cm), and GPH Z-score at diagnosis of IGHD. Growth charts proposed by the CDC were used. All children were pre-pubertal (Tanner stage 1) at baseline. Final height was defined as the height achieved by confirming a GV below 2 cm/year during somatropin treatment and bone age of 13 years in girls and 14 years in boys. The genetic potential height was defined as the GPH ± 1 SD, representing the final height target. The effect of somatropin was assessed through final height, height Z-score, total height gain, and -zGPH-zFH (difference between GPH and final height). GV was assessed annually throughout somatropin treatment. Baseline parameters and final height were compared according to sex.

The somatropin administered was part of the basic list of drugs provided by the Mexican Social Security Institute to its beneficiaries. The initial dose of somatropin was 25-50 µg/kg/day according to the recommendations established by the Endocrine Society and the GH Research Society[6]. This study was approved by the Local Health Research Committee No. 3603 of the Mexican Social Security Institute, N° R2018-3603-006.

GH and IGF-1 concentrations were determined by chemiluminescence (Liaison, DiaSorin). The international standard WHO/NIBSC 95/574 was used to calibrate the GH assay and WHO/NIBSC 02/254 for the IGF-1 assay.

Statistical analysis

Categorical variables were reported in proportions and frequencies. Quantitative variables were described as mean ± SD or median and interquartile range (IQR), according to their distribution. Quantitative variables were analyzed using T-Student, Mann-Whitney U, or Wilcoxon tests. The correlation coefficient of Pearson or Spearman was used to evaluate associations according to the type of variable and linear regression was performed to corroborate the association. A p-value < 0.05 was considered statistically significant and the SPSS v.24 and STATA v.13 statistical software were used for the analysis.

Results

Out of 306 patients with GH deficiency and treated with somatropin, 112 had a diagnosis of severe IGHD. During follow-up, 36 patients dropped out of the study due to change of address to another region of the country or loss of social security in the institution, 18 patients did not have adequate therapeutic adherence, and 6 patients presented adverse drug reactions (hyperglycemia). 50 patients with severe GH deficiency were monitored until reaching the final height and were included in the analysis.

Auxological and demographic characteristics

40% (n = 20) of the patients were girls; all were in Tanner stage I before somatropin initiation. Chronological age at diagnosis of IGHD was 10.3 ± 2 years, bone age was 8.3 ± 2 years, and height was 126.6 ± .5 cm (Z-score -2.6 ± 0.4). GPH was 161 ± 7.1 cm (Z-score -1.15 ± 0.81); in boys was 165.7 ± 4.1 cm, while in girls was 153.9 ± 4.2. 20% (n = 10) of the cases presented familial short stature. The GH after stimulation test and basal IGF-1 values for the diagnosis of severe GH deficiency were 0.20 µg/L (IQR 0.03-0.4) and 118 ng/mL (IQR 80.3-130), respectively.

According to sex, there was only a statistically significant difference in GPH (boys 165.7 ± 4.1 vs girls 153.9 ± 4.2 cm; p = 0.001). Table 1 shows the auxological characteristics according to sex of the total sample.

Effects of somatropin on auxological characteristics at final height

Final height was 155.5 ± 8.6 cm, with a Z-score of -1.6 ± 0.7 (boys: 159.7 ± 7.1 cm, Z score -1.5 ± 0.68; girls: 149.1 ± 6.4 cm, Z-score -1.8 ± 073). The age at reaching final height was 14.8 ± 1.2 years. 92% (n = 46) of the cases reached their genetic potential height, with a Z-score for height gain of 1 ± 0.6 cm (total height gain 28.7 ± 10.3 cm). The treatment time to reach final height was 4.1 ± 1.5 years. 4% (n = 2) reached final height at the first year of somatropin treatment, 22% (n = 11) at the second year, 22% (n = 11) at the third year, 42% (n = 21) at the fourth year, 6% (n = 3) at the fifth year, and 4% (n = 2) at the sixth year. The required dose of somatropin to achieve final height was 33 ± 0.5 µg/kg/day. During follow-up, chronological and bone age progressed similarly. At final height, there was no difference between chronological and bone age [chronological age 14.9 (14.6-15.4) vs bone age 14.1 (13.7-15.1) years; p = 0.75].

According to sex, there was a statistically significant difference in the age at achieving final height (boys: 15.3 ± 1 vs girls: 14 ± 1.1 years; p = 0.001), total height gain (boys: 31.4 ± 10.8 vs girls: 24.7 ± 8.1 cm; p = 0.001), and final height (boys: 159.7 ± 7.1 vs girls: 149.1 ± 6.4 cm; p = 0.001), however, there was no difference in the Z-score for height. Table 1 shows the auxological characteristics at final height. The best GV was observed during the first year of treatment. Table 2 shows the GV per year according to height and Z-score for height during treatment. Regarding GV in the first year of treatment, there was a positive correlation between initial height (r = 0.49; p = 0.001) and initial height Z-score (r = 0.67; p = 0.001), confirmed

by the linear regression model (initial height b = 0.27; p = 0.032 and final height Z-score b = 0.47; p = 0.001).

At the beginning of the study, all patients were in prepubertal stage. The age of pubertal onset was 13.9 years (12.9-15.8). The onset of puberty was observed in 6% (n = 3) of the patients at the first year of somatropin treatment, with a cumulative frequency of 24% (n = 12) at the second year, 62% (n = 31) at the third year, 84% (n = 42) at the fourth year, 96% (n = 48) at the fifth year, and 100% (n = 50) at the sixth year. All patients initiated puberty before reaching their final height.

In the study, there was a positive correlation of final height with GPH (r = 0.30; p = 0.03) and somatropin dose (r = 0.63; p = 0.001), confirmed by linear regression model (GPH b = 0.71; p = 0.001 and somatropin dose b = 0.30; p = 0.028). In addition, there was no correlation between final height and GH peak after stimulation test (r = 0.1; p = 0.89) or IGF-1 at diagnosis of IGHD (r = 0.5; p = 0.39), nor between somatropin dose and GH peak after stimulation test (r = 0.11; p = 0.41) or IGF-1 at diagnosis of IGHD (r = 0.2; p = 0.74).

Auxological and biochemical characteristics according to the achievement of the genetic potential height

Table 3 shows the auxological characteristics of the four patients who did not achieve the genetic potential height. Adequate therapeutic adherence was confirmed in all 4 cases. When comparing the auxological and biochemical characteristics of these patients with those who achieved the genetic potential height, differences were observed in the genetic potential height [161.5 (159.5-167.5) vs. 153 (147-158) cm; p = 0.05], final height [159 (156-162) vs 152 (145.2-156.2) cm; p = 0.04], Z-score for height (-1.2 vs -2.23; 0.001), the ΔzGPH - zFH {0.01 (-0.24-0.16) vs -3.4 [-3.5 - (-2.8)]; p = 0.001}, and the time to reach final height [3.5 (2-5) vs 5 (5-6) years; p = 0.001] (table 3).

Among the children who reached the genetic potential height (n = 46; boys n = 29; girls n = 17), there was a significant statistical difference in the genetic potential height [boys 165.5 (163.5-168.5) vs girls 153.5 (150.5-156) cm; p = 0.001] and in the final height [boys 161.6 (155-165) vs girls 152 (146.5-154.1) cm; p = 0.001] according to sex.

Among patients who did not reach the genetic potential height, there was a positive correlation between final height and GPH (r = 0.80; p = 0.020), with no evidence of correlation with the rest of the variables included in table 3.

Discussion

Different studies have reported the effect of somatropin on auxological characteristics in children with GH deficiency, independently of its origin. Treatment with somatropin has been shown to improve GV and

Table 1. Auxological characteristics of the patients included in the analysis (n = 50)

	Total (n = 50)	Boys (n = 30)	Girls (n = 20)
Basal auxological characteristics			
Chronological age (years)	10.3 ± 2	10.6 ± 2.1	10 ± 1.8
Bone age (years)	8.3 ± 2	8.2 ± 2.2	8.3 ± 1.8
Basal height (cm)	126.6 ± 9.5	128.3 ± 9.8	124 ± 8.7
Z-score for height (cm)	-2.6 ±0.4	-2.5 ± 0.5	-2.8 ± 0.5
Genetic potential height (cm)	161 ± 7.1	**165.7 ± 4.1***	**153.9 ± 4.2***
Z-score for GPH	-1.15 ± 0.8	-1.08 ± 0.8	-1.26 ± 0.7
Auxological characteristics at final height			
Chronological age (years)	14.8 ± 1.2	**15.3 ± 1***	**14 ± 1.1***
Height (cm)	155.5 ± 8.6	**159.7 ± 7.1***	**149.1 ± 6.4***
Z-score for height (cm)	-1.6 ± 0.7	-1.5 ± 0.68	-1.8 ± 0.73
ΔzGPH-zFH	0.12 ± 0.8	-0.17 ± 0.7	-0.28 ± 0.9
Somatropin doses (µg/kg/day)	33 ± 0.5	33 ± 0.5	33 ± 0.4
Height gain (cm)	28.7 ± 10.3	**31.4 ± 10.8***	**24.7 ± 8.1***
Time to reach final height (years)	4.2 ± 1.5	5.3 ± 1	4 ± 1.2

Quantitative variables reported as mean ± standard deviation or median (interquartile range) according to their distribution. *p < .001 between boys and girls. GPH: Genetic potential height (cm). FH: Final height.

Table 2. Annualized growth velocity, height and Z-score for height during somatropin treatment

Years of treatment	n	Annualized growth velocity (cm)	Height (cm)	Z-score for height
1° year	50	9 ± 3.8	135.6 ± 10.8	-2.1 ± 0.6
2° year	48	7.1 ± 2.9	142.3 ± 10.4	-1.76 ± 0.1
3° year	37	7 ± 2.3	146.1 ± 9	-1.66 ± 0.8
4° year	26	6.9 ± 3	150.6 ± 9.2	-1.49 ± 0.8
5° year	5	8.5 ± 7.6	153 ± 4.4	-0.82 ± 1.4
6° year	2	6.1 ± 4.3	160 ± 7	-0.06 ± 2.5

Quantitative variables reported as mean ± standard deviation or median (interquartile range) according to their distribution.

final height in patients with IGHD from different populations around the world[7-16], however, information on these results is scarce in Latin American populations. There are multiple difficulties in the diagnosis and treatment of GH deficiency in Latin America, among which stand out the absence of updated national charts for the evaluation of growth, the lack of accessibility to laboratory studies for the evaluation of the GH-IGF-1 axis, and the limitations to initiate and maintain treatment with somatropin[17]. In our study, we corroborated that somatropin treatment improves GV and short stature in Mexican children with IGHD.

The main objective when initiating treatment with somatropin is to achieve the genetic potential height. The percentage of children with IGHD who achieve this ranges from 65 to 83%[7-16], depending on the population studied. In our population, this is the first published study that reports the percentage of children with IGHD who achieve the genetic potential height upon treatment with somatropin, with a frequency similar to that reported in other populations (92%)[7,16].

Gjikopulli et al. have reported a lower percentage of patients with IGHD achieving the genetic potential height (55%)[12]. In contrast to this, in our series somatropin initiation was at younger chronological and bone age, only patients with adequate therapeutic adherence were included, and the somatropin dose and duration of treatment were higher.

As a finding similar to that reported in other populations[7-16], the Z-score for GPH in our patients was found to be within 2 SDs of the population mean, with a corrected Z-score within -1.5 SD for GPH.

The dose and duration of somatropin treatment to achieve the genetic potential height in our study were similar to that recommended in international guidelines; most children were treated for 4 years at a dose of 33 ± 0.5 µg/kg/d, highlighting the importance of continuous and long-term treatment to achieve the therapeutic effect of somatropin.

The highest GV and height gain evidenced in this study was during the first year of somatropin initiation, with a second peak in the fifth year. The GV showed a positive association with initial height and Z-score, so these parameters could be considered possible predictors of therapeutic response in our population. It is important to note that most of the children who reached final height at the 5th year of treatment started puberty during this period, so we do not rule out a relationship between the pubertal peak and the acceleration of GV, in addition to that these patients had already presented an acceleration of growth within the first year of treatment. During treatment, bone and chronological age advanced similarly until the final height was reached.

Despite the differences in GPH, final height, chronological age, and total height gain according to sex, there was no difference in the Z-score of final height, indicating that, regardless of sex, treatment with somatropin allows reaching an optimal final height.

Factors associated with final height in children with GH deficiency treated with somatropin include weight[8,14], length at birth[6], height at the start of treatment[8,14], GPH, GV during the first and second year of treatment[8], body mass index, and somatropin dose and duration[14]. In our study, we observed that GPH and somatropin dose are associated with final height, confirming the importance of genetic potential and dose-dependent effect in achieving final height prognosis.

Although somatropin is considered an effective drug[18], some patients do not achieve the genetic potential height, observing in our case a low percentage (8%). In our country, there is a high prevalence of short stature, mainly related to unfavorable living conditions[19]. An interesting finding was the coexistence of familial short stature and IGHD in one-fifth of the included population. Of these patients, 3 of 4 did not reach their genetic potential height. Patients who did not reach their genetic potential height had a lower GPH compared with those who did, highlighting

Table 3. Auxological and biochemical characteristics according to the achievement of the genetic potential for height

	Achievement of genetic potential height (n = 46)	Without achievement of genetic potential height (n = 4)	p
Basal auxological characteristics			
Chronological age (years)	12.2 (9.1-13)	11.1 (10.5-11.7)	0.42
Bone age (years)	10 (7-12)	8 (7.5-12)	0.69
Basal height (cm)	131.8 (121-134.9)	131.5 (121.3-136)	0.76
Z-score for height (cm)	-2.5 [-2.78 – (-2.34)]	-2.3 [-2.8 – (-2.0)]	0.31
Genetic potential height (cm)	Total: 161.5 (159.5-167.5) De acuerdo al sexo: Niños (n = 29): 165.5 (163.5-168.5) Niñas (n = 17): 153.5 (150.5-156)	Total: 153 (147-158) De acuerdo al sexo: Niños (n = 1): 167 Niñas (n = 3): 155 (152.3-157.5)	0.05*
Peak GH post stimulation test	0.20 (0.05-0.30)	0.35 (0.17-1.0)	0.39
Basal IGF-1	118 (109-129)	123 (113.5-130)	0.59
Auxological characteristics at final height			
Chronological age (years)	15.4 (15-15.5)	14.9 (15.1-15.3)	0.49
Bone age (years)	14.3 (13.9-15.2)	14.4 (13.8-15.0)	0.70
Age at onset of puberty	14.9 (14.2-15.7)	14.6 (14.1-16)	0.29
Height (cm)	Total: 159 (156-162) De acuerdo al sexo: Niños (n = 29): 161.6 (155-165) Niñas (n = 17): 152 (146.5-154.1)	Total: 152 (145.2-156.2) De acuerdo al sexo: Niños (n = 1): 155 Niñas (n = 3): 144.5 (142.2-145.1)	0.04*
Z-score for height (cm)	Total: -1.2 [-1.25 – (-0.85)] De acuerdo al sexo: Niños (n = 29): -1.5 [-2.0– (-1.03)] Niñas (n = 17): -1.6 [-1.9 – (-1.1)]	Total: -1.5 [-2.1 - (-0.3)] De acuerdo al sexo: Niños (n = 1): -2.6 Niñas (n = 3): -2.9 [-3.0 - (-2.7)]	0.001*
ΔzGPH-zFH	Total: 0.01 (-0.24 - 0.16) De acuerdo al sexo: Niños (n = 29):0.06 [-0.3 - 0.34] Niñas (n = 17): 0.11 [-0.24 - 0.34]	Total: -3.4 [-3.5 – (-2.8)] De acuerdo al sexo: Niños (n = 1): -1.33 Niñas (n = 3): -1.72 [-2.14 - (-1.12)]	0.001*
Somatropin doses (µg/kg/day)	42 (39-42)	31 (29-34)	0.93
Time to reach final height (years)	3.5 (2-5)	5 (5-6)	0.001*

Quantitative variables reported as mean ± standard deviation or median (interquartile range) according to their distribution. *Statistical significance p < 0.001. GPH: Genetic potential height (cm). FH: Final height. GH: Growth hormone. IGF-1: Insulin-like Growth Factor-1.

that not only did they not reach their genetic potential, but also their final height was well below the predicted height. In our study, GPH was one of the factors associated with final height, representing a possible predictor of response to treatment, as well as supporting the importance of genetic potential in height prognosis.

Despite controlling the inclusion of IGHD patients without coexisting diseases and corroborating adequate therapeutic adherence, considering the limitation of more sensitive and specific pharmacovigilance methods, one factor that could not be ruled out was the presence of antibodies against GH, which can limit the therapeutic effect of somatropin.

The main strength of our study was the inclusion of a specific population (children with IGHD), without comorbidities, which reduced the possibility of biases caused by the direct effect of other pathologies on linear growth and final height. On the other hand, limitations include the retrospective nature of the study, the relatively small sample size derived from our selection and exclusion criteria, as well as the limited resources for molecular and genetic studies.

The cut-off points used in our study for the diagnosis of GH deficiency were based on international recommendations established by the Endocrine Society and GH Research Society[6], however, recent recommendations propose using GH after stimulation test cut-off points < 7 µg/L (even < 5 µg/L) for the diagnosis of GH deficiency and < 3 µg/L for severe deficiency[20], therefore these may be considered during clinical practice. We propose to continue prospective studies in Latino patients with GH deficiency, with the

application of stricter GH after stimulation test cut-off points, along with pharmacovigilance, and safety and efficacy of long-term somatropin treatment in order to reduce the limitations of this study and increase knowledge in this understudied population.

In conclusion, somatropin treatment allows normalization of GV and achieving final height within the genetic potential in most Mexican children with IGHD. Somatropin induces an increase in GV, especially during the first year. Final height is associated with GPH and somatropin dose, highlighting the importance of the genetic potential and the dose-response effect of somatropin in establishing height prognosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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