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FINAL HEIGHT IN CHILDREN WITH IDIOPATHIC GROWTH HORMONE DEFICIENCY TREATED WITH RECOMBINANT HUMAN GROWTH HORMONE: THE BELGIAN EXPERIENCE

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KEYWORDS: Growth hormone deficiency; Growth hormone treatment ; Final height ; Idiopathic hypopituitarism ; Puberty

ABSTRACT

Background: The growth response to recombinant hGH (rhGH) treatment and final height of 61 Belgian children (32 boys) with idiopathic growth hormone deficiency (GHD) were studied. ***Patients/Methods:*** Two patient groups were compared: Group 1 with spontaneous puberty (n = 49), Group 2 with induced puberty (n = 12). The patients were treated with daily subcutaneous injections of rhGH in a dose of 0.5-0.7 IU/kg/week (0.17-0.23 mg/ kg/week) from the mean ± SD age of 11.9 ± 3.1 years during 5.1 ± 2.1 years. ***Results:*** rhGH treatment induced a doubling of the height velocity during the first year and resulted in a normalisation of height in 53 (87%) patients. Final height was -0.7 ± 1.1 SDS, being 170.4 ± 7.2 cm in boys and 158.0 ± 6.4 cm in girls. Corrected for mid-parental height, final height was 0.0 ± 1.1 SDS. Ninety-two percent of the patients attained an adult height within the genetically determined target height range. Although height gain during puberty was smaller in the patients with induced puberty (boys: 17.1 ± 7.0 cm vs. 27.5 ± 6.6 cm ($p < 0.005$); girls: 9.6 ± 7.4 cm vs. 22.2 ± 6.1 cm ($p < 0.005$)), no differences in final height after adjustment for mid-parental height were found between patients with spontaneous or induced puberty. ***Conclusions:*** We conclude that patients with idiopathic GHD treated with rhGH administered as daily subcutaneous injections in a dose of 0.5-0.7 IU/kg/week reach their genetic growth potential, resulting in a normalisation of height in the majority of them, irrespective of spontaneous or induced puberty.

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Introduction

Treatment of patients with growth hormone deficiency (GHD) with growth hormone (GH) was introduced in Belgium in 1969 [1]. Until 1985, the patients were treated with pituitary-extracted human GH (hGH). In those days hGH supplies were limited and patients were treated with 2- or 3-weekly intramuscular injections of 4-8 international units (IU) of hGH. The final height results were suboptimal, being 162.9 ± 7.2 cm for boys and 149.8 ± 6.7 cm for girls, equalling -1.7 ± 1.3 SDS [1, 2].

In 1985 treatment with pituitary extracted hGH was interrupted and from then on all GHD patients were treated with recombinant hGH (rhGH). As several studies have shown that daily administration of rhGH resulted in a better growth response [3-5] and as the supply of rhGH was potentially unlimited, rhGH was administered as daily subcutaneous injections in a dose of 0.5-0.7 IU/kg/week (0.17-0.23 mg/kg/week). So far, only a few studies reported final height data of patients with idiopathic GHD treated only with daily injections of rhGH [6-9]. In this paper, we report on the growth response to the daily administration of rhGH, we present final height data of 61 Belgian patients with idiopathic GHD and we compared the results obtained in patients with spontaneous puberty with those with induced puberty.

Patients and Methods

From the database of the Belgian Study Group for Paediatric Endocrinology, containing auxological and biochemical data of about 600 GH-treated patients with childhood onset GHD, followed in the departments of paediatric endocrinology of the 7 Belgian university hospitals, patients fulfilling the following inclusion criteria were selected: (1) having GHD, defined by auxological and biological criteria (height velocity below the 10th percentile, peak GH values after two GH stimulation tests (glucagon, insulin) less than 10 ng/ml); (2) having idiopathic GHD, defined as the absence of any evidence for a CNS tumour or a pituitary or hypothalamic malformation on cranial CT scanning ; (3) being treated solely with daily injections of rhGH until final height; (4) having attained final height, i.e. height velocity during the preceding year was less than 2 cm or when growth during the last 6 months was less than 1 cm.

Sixty-one patients (32 boys) fulfilled all the inclusion criteria. Twenty-five patients (18 boys) with idiopathic GHD were excluded from the present analysis: 16 patients voluntary stopped rhGH treatment before final height was reached and were lost for follow-up, and in 9 patients rhGH treatment was stopped because a repeated GH stimulation test during treatment showed normal GH values [10].

Treatment with rhGH started between June 1987 and March 1994 and was stopped between March 1991 and March 1999. The rhGH dose used at the initiation of hGH treatment was 0.7 IU/kg/ week before 1992, and thereafter 0.5 IU/kg/week. The amount of injected rhGH was adapted every 3

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months according to body weight in order to keep the dose as close as possible to the initial dose. So, the mean ± SD rhGH dose during treatment was 0.63 ± 0.10 IU/kg/ week.

Two patient groups were formed: Group 1: patients with sponta-neous puberty (n = 49, 25 boys), and Group 2: patients with induced puberty due to an associated gonadotrophin (GND) deficiency (n = 12; 7 boys). All but 2 patients of group 1 had isolated GHD: 1 patient had also TSH and ADH deficiencies and 1 patient had associated TSH deficiency. Due to a delayed onset of puberty, 5 boys of group 1 were temporarily treated with testosterone-oenanthate injections (25 mg every 2 weeks) for 8-24 months from the mean age of 14.8 ± 1.5 years. All patients of Group 2 had multiple pituitary hormonal deficiencies (7 associated TSH, ACTH and GND deficiency; 1 TSH and GND deficiency; 1 ADH and GND deficiency; 3 GND deficiency). They all received appropriate substitution therapy. In boys puberty was induced with intramuscular injections of testosterone- oenanthate every 2 weeks and girls received daily oral ethinyloestradiol.

Most of the patients started rhGH treatment before magnetic resonance imaging (MRI) was performed on a regular basis. Twenty-two patients of Group 1 and 9 of Group 2 underwent a cerebral MRI. In Group 1, 1 patient had a pituitary stalk interruption syndrome, characterised by an ectopic posterior hypophysis, an interruption of the pituitary stalk and hypoplasia of the anterior hypophysis. Two patients had an ectopic posterior hypophysis with a visible stalk. The 19 other patients had a hypoplasia of the anterior hypophysis or a normal MRI. In Group 2, 6 patients had a pituitary stalk interruption syndrome and 1 patient an ectopic posterior hypophysis with a thin pituitary stalk. In 2 patients the anterior hypophysis was hypoplastic.

The patients were seen every 3 months in the outpatient clinic. Height was measured with a Harpenden stadiometer. Height data were expressed as standard deviation scores (SDS) using the Tanner references [11]. Pubertal development was evaluated according to Tanner [12] and the testicular volume was measured with a Prader orchidometer [13]. Onset of puberty was defined by a testicular volume 64 ml in boys and by the presence of breast stage 2 (B2) in girls. Bone age was read by the individual investigators using the methods of Tanner and Whitehouse [14] or Greulich and Pyle [15]. If the bone age was estimated by the Greulich and Pyle method, a correction was made by adding 0.9 years, based on the mean difference between the 2 methods [16]. Birth weight and birth length SDS were calculated using the Swedish references [17]. Mid-parental height SDS was calculated as: (height SDSfather+ height SDSmother)/1.61 [18, 19] and the parent-specific lower limit of height SDS was calculated as: (0.5 X mid-parental height SDS) - 1.73 [19].

Results are expressed as mean ± SD or median (range) as indi-cated. Comparison between 2 groups were done by the unpaired t test or the Mann-Whitney U-test. Simple and multiple linear regres-sion analyses were performed on the combined data of the 2 treat-ment groups in order to analyse the relationship between various auxological parameters and final height. A p value < 0.05 was considered as significant.

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Results

PATIENT CHARACTERISTICS AT START OF TREATMENT

Table 1 shows the baseline characteristics of the 61 patients with idiopathic GHD treated with rhGH. Chronological age at start of treatment was 11.9 ± 3.1 years and bone age was 9.9 ± 3.1 years. The patients with induced puberty were older than those with spontaneous puberty and bone maturation was more retarded. Fourteen patients (29%) of Group 1 were in puberty at the time rhGH treatment was initiated (B2 or G2: n = 9; B3 or G3: n = 4; G4: n = 1). Height at start of treatment was -2.7 ± 0.8 SDS and height deficit, calculated as the difference between mid-parental height SDS and height SDS at the start of treatment amounted to 2.1 ± 1.2. Height velocity during the year before treatment was 3.8 ± 1.3 cm/year. There were no differences in height SDS, height deficit or height velocity between girls and boys, neither between patients with or without spontaneous puberty. Mean birth weight of the patients was below the normal references. Birth length was shorter in the patients with spontaneous puberty than in those with induced puberty. Eight patients (16%) with spontaneous puberty and 1 patient (8%) with induced puberty had an intra-uterine growth retardation (birth weight SDS <-2.0). Mid-parental height SDS of the patients with spontaneous puberty was lower than the population mean ($p < 0.001$). Nine (75%) of the patients with induced puberty and 19 (39%) of those with spontaneous puberty had a peak GH level < 5 µg/l, suggesting a more severe degree of GHD in the patients with induced puberty.

PATIENT CHARACTERISTICS DURING RHGH TREATMENT AND AT FINAL HEIGHT

Table 2 shows the auxological data during rhGH treatment. Mean duration of rhGH treatment was 5.1 ± 2.1 years. In both groups height velocity increased more than double during the first year of treatment. During the second year of treatment, height velocity decreased but remained above pretreatment levels.

In the prepubertal patients of Group 1 (n = 35) puberty started at the age of 13.3 ± 1.6 years in boys and 11.8 ± 1.4 years in girls. Puberty was induced in the patients of Group 2 at the age of 17.2 ± 2.3 years in boys and 14.9 ± 2.0 years in girls, significantly later than the onset of spontaneous puberty in the patients of Group 1 ($p < 0.005$).

The patients of Group 1 were about 0.5 SD shorter at the onset of puberty; the difference was, however, not statistically significant. Height gain during puberty was greater in the patients with spontaneous puberty than in those with induced puberty: the boys of Group 1 grew 27.5 ± 6.6 cm whereas the boys of Group 2 grew 17.1 ± 7.0 cm ($p < 0.005$); Group 1 girls gained 22.2 ± 6.1 cm during puberty whereas Group 2 girls gained only 9.6 ± 7.4 cm ($p < 0.005$).

Treatment was stopped at the age of 18.0 ± 1.5 years in boys and 15.9 ± 1.4 years in girls. Final height was obtained at the age of 19.5 ± 2.1 years in boys and 16.6 ± 1.7 years in girls. Final height was 169.0 ± 7.1 cm in boys with spontaneous puberty and 175.5 ± 5.1 cm in those with induced puberty ($p < 0.05$). The girls with spontaneous puberty achieved a final height of 157.3 ± 6.2 cm and

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those with induced puberty 161.7 ± 6.4 cm. Figure 1a shows the height SDS at start of treatment and final height SDS for the patients with spontaneous puberty and figure 1b for those with induced puberty. All the patients with induced puberty and 41 out of 49 of those with spontaneous puberty (84%) reached a final height above the -1.88 SDS (or 3rd percentile). Forty-five patients with spontaneous puberty (92%) and 11 patients with induced puberty (92%) achieved a final height above the parent specific lower limit of height. Final height SDS was higher in patients with induced puberty than in those with spontaneous puberty. However, after correction of final height SDS for mid-parental height SDS there were no differences in final height between the 2 patient groups: 0.0 ± 0.9 SDS for the patients with spontaneous puberty and 0.1 B 1.6 SDS for those with induced puberty.

The results of the simple linear regression analysis are shown in table 3. Mid-parental height SDS was the variable most strongly related to final height. Other variables related significantly with final height were birth weight (SDS) and birth length (SDS), height SDS at the start of treatment and at the onset of puberty, and height velocity during the first and second year of rhGH treatment. Chronological age or bone age at start of treatment and the onset of puberty, gender, bone age delay, height deficit, peak GH levels after stimulation, duration of rhGH treatment, and the rhGH dose were not related to final height.

Multiple linear regression analysis, including the variables identified in the simple linear regression analysis, resulted in the following regression equation: final height (SDS) = 0.72 + [0.46 (95% CI: 0.22-0.69) X mid-parental height SDS ($p < 0.0005$)] + [0.32 (0.11-0.52) X birth weight (SDS) ($p < 0.005$)] + [0.31 (0.03-0.58) X height SDS at the start of rhGH treatment ($p < 0.05$)] ($R^2 = 0.43$; $p < 0.0001$).

Table 1. *Baseline characteristics of rhGH-treated GHD patients with spontaneous or induced puberty*

	Spontaneous puberty		Induced puberty	
	boys	girls	boys	girls
Number	25	24	7	5
Age at start rhGH	12.4±2.6	10.6±2.6	14.4±4.1	11.5±2.2
Bone age at start	10.2±3.0 (n= 20)	9.0±3.0 (n = 21)	12.8±2.2 (n = 6)	7.9±2.0 (n = 3)
Bone age delay, years	1.8±1.3 (n = 41)		3.3±1.0 (n = 9)***	
Prepubertal/pubertal	35/14		12/0	
Height at start, SDS	-2.7±0.7		-2.9±1.2	
Mid-parental height SDS - height SDS at start	1.9±1.0		2.8±1.7	
Height velocity, cm/year	3.9±1.3 (n = 48)		3.5±1.4 (n = 11)	
Birth weight, SDS	-1.0±1.1 (n = 48)		-0.4±1.1 (n = 11)	
Birth length, SDS	-0.8±1.0 (n = 41)		0.5±1.2 (n = 7)**	
Mid-parental height, SDS	-0.8±0.9		-0.1±1.3	
GH peak after glucagon stimulation, µg/l[a]	5.8 (0.4-9.7) (n = 48)		1.3 (0.6-8.7)**	
GH peak after insulin stimulation, µg/l[a]	4.4 (0.2-9.3)		1.3 (0.1-8.4) (n = 10)*	

[a] Median (range).

*p < 0.05; ** p < 0.01; *** p < 0.005 (induced puberty vs. spontaneous puberty).

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Table 2. *Characteristics of patients with idiopathic GHD during rhGH treatment and at final height*

	Spontaneous puberty		Induced puberty	
	boys	girls	boys	girls
Duration of rhGH treatment, years	5.2±2.2		4.7±2.2	
Height velocity 1st year of treatment, cm/year	9.5±2.2		8.9±3.2	
Height velocity 2nd year of treatment, cm/year	7.9±2.1		8.0±2.3 (n = 11)	
Age at onset of puberty, years	13.3±1.6	11.8±1.4	17.2±2.3***	14.9±2.0***
Height at onset of puberty, SDS	-1.9±0.8		-1.4±1.2	
Height gain during puberty, cm	27.5±6.6	22.2±6.1	17.1±7.0***	9.6±7.4***
Age at treatment interruption, years	17.6±1.0	15.8±1.3	19.5±2.0***	17.0±1.5
Age at final height, years	19.1±1.8	16.2±1.4	21.0±2.8*	18.5±2.2**
Final height, cm	169.0±7.1	157.3±6.2	175.5±5.1*	161.7±6.4
Height at treatment interruption, SDS	-0.8±0.9		-0.3±1.1	
Final height, SDS	-0.8±1.0		0.0±0.9*	
Final height SDS - mid-parental height SDS	0.0±0.9		0.1±1.6	

*p < 0.05; ** p < 0.01; *** p < 0.005 (induced puberty vs. spontaneous puberty).

Figure 1. a *Height SDS at the start of rhGH treatment and final height SDS in patients with spontaneous puberty.* ***b*** *Height SDS at the start of rhGH treatment and final height SDS in patients with induced puberty.*

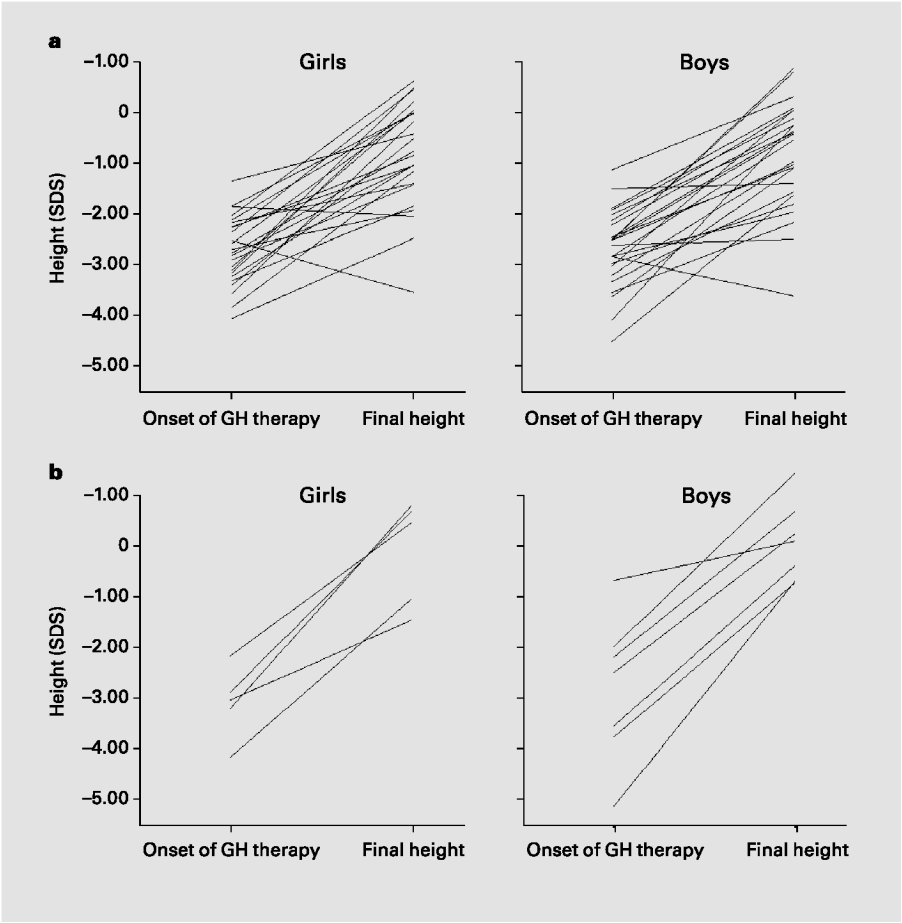

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Table 3. *Results of simple linear regression analysis with final height SDS as dependent variable*

	R	p
Mid-parental height, SDS	0.47	<0.0005
Birth weight, SDS (n = 59)	0.43	<0.001
Height at onset of puberty, SDS (n = 55)	0.33	<0.02
Birth length, SDS (n = 48)	0.31	<0.05
Height velocity during the 2nd year of rhGH treatment, cm/year (n = 60)	0.30	<0.05
Height at start of rhGH treatment, SDS	0.28	<0.05
Height velocity during the 1st year of rhGH treatment, cm/year	0.27	<0.05

Discussion

In this study we report the growth response to daily injections of rhGH in a dose of 0.5-0.7 IU/kg/week and final height of 61 patients with idiopathic GHD. We found that rhGH treatment induced a doubling of the height velocity during the first year and resulted in a normalisation of height in most of the patients. Final height was -0.7 ± 1.0 SDS, being 170.4 ± 7.2 cm in boys and 158.0 ± 6.4 in girls. Corrected for mid-parental height, final height was 0.0 ± 1.1 SDS, illustrating that most of the patients attained an adult height within the genetically determined target height.

It is worthwhile to notice that the studied patients were relatively old at the start of rhGH treatment and that the duration of rhGH therapy was relatively short. This is due to the fact that only patients treated solely with daily injections of rhGH, a treatment regimen that started in 1987, were included in the analysis. Children who started rhGH treatment at a younger age have not yet reached final height and did not fulfil the inclusion criteria. Nevertheless, in spite of the old age at start of treatment and the short duration of rhGH treatment the final height outcome seems satisfying. It remains to be shown whether a longer period of rhGH treatment will result in even better results.

Our results are much better than those reported by our group in 1987 [1]. In 34 GHD patients, of whom 6 had isolated GHD and 28 multiple pituitary hormonal deficiencies, treated with 2 or 3 weekly injections of extracted hGH, final height was -1.7 ± 1.3 SDS, being 162.9 ± 7.2 cm in the boys and 149.8 ± 6.7 cm in the girls. Studies on final height in GHD reported in the literature during the last 5 years show mean final height results between -3.0 and -0.7 SDS [6-9, 20-26]. In most of these studies patients were treated with different treatment regimens going from low doses of rhGH administered 3 times a week to daily high doses of rhGH adapted as a function of body weight.

So far, only 4 studies report final height data of patients with idiopathic GHD treated exclusively with daily injections of rhGH. Bramswig et al. [6] treated 36 GHD patients, of whom 28 had idiopathic GHD, with subcutaneous rhGH 6-7 times/week in a dose of 13.7 ± 1.1 IU/m^2/week (equivalent to 0.5 IU/kg/week) and found a mean final height of -1.1 ± 0.9 SDS (compared to Swiss growth references [27]). Blethen et al. [7] reported a final height SDS of -0.7 ± 1.4 SDS (compared to American growth references [28]) in 121 GHD patients (102 idiopathic GHD) treated randomly with daily or three times a week rhGH. The injection frequency did not seem to influence final height.

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Cacciari et al. [8] observed a mean final height of -1.3 ± 0.9 SDS (Tanner references [11]) in 83 patients with isolated idiopathic GHD treated with daily injections of rhGH in a dose varying between 0.53 and 0.70 IU/kg/week. In a subgroup of KIGS consisting out of 69 Swedish idiopathic GHD patients treated with daily rhGH injections in a dose of ± 0.66 IU/kg/week final height was -0.3 SDS (Tanner references [11]) and all patients reached their target height range [9]. Taken together, our results and those from the recent literature clearly show that patients with idiopathic GHD can reach a normal final height when they are treated with daily injections of rhGH in a dose between 0.5 and 0.7 IU/kg/ week.

Moreover, most of the patients attained a final height within the target range. So it turns out that the genetic potential can be fully restored and that adult height of the child with idiopathic GHD is depending on the same genetic influences as in normal children [18]. Indeed, in agreement with other studies on final height in GHD patients [8, 9, 22], we found that mid-parental height had the greatest influence on final height in response to rhGH therapy. A comparable strong relationship between parental height and the adult height of the child has been reported in normal children [18] and in girls with Turner syndrome without [29] or with rhGH treatment [30]. In agreement with the data from the literature we found that birth weight SDS [9, 31] and the height at start of rhGH treatment [8, 9] were also positively related to final height SDS.

In the patients with idiopathic GHD, however, it remains to be shown whether the good final height results are the consequence of rhGH treatment. Indeed, recent studies have shown that a considerable number of patients, diagnosed as having idiopathic GHD during childhood, have a normal GH secretion when re-evaluated at a later age [32, 33]. In our patient series we also found that when retested at adult age only 24% of the patients with idiopathic GHD still were GHD, defined as a stimulated GH response < 5 ng/ml [10, 34]. As the spontaneous growth process in patients with 'transient' GHD is unknown, it is quite impossible to sort out the respective importance of pubertal catch-up and the treatment effect of rhGH.

Puberty was induced relatively late in our patients. Bourguignon et al. [2] previously reported that children with GHD and GND had an older age at onset of puberty that resulted in an increase of height at onset of puberty followed by a decrease of pubertal height gain so that final height was not affected when compared with children with spontaneous puberty. In the present study patients with induced puberty reached a taller final height than those with spontaneous puberty, and this in spite of a smaller height gain during puberty. The patients with induced puberty did have multiple pituitary hormonal deficiencies, a more severe degree of GHD, and different baseline auxological parameters. So any comparison with patients with idiopathic GHD should be interpreted very cautiously. Moreover, the observed difference in final height completely disappeared when mid-parental height was taken into account. This finding is in agreement with the observations of Blethen et al. [7] who also did not found an adverse effect of spontaneous puberty on final height of GHD patients. In contrast, Mericq et al. [35] recently reported that adding a luteinizing hormone- releasing hormone analog to rhGH treatment of pubertal GHD patients increased final height. Further studies are needed to evaluate whether postponing the onset of

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puberty, which also has important psychosocial consequences [36], is really beneficial for final height.

In conclusion, our data show that patients with idiopathic GHD treated with rhGH administered as daily subcutaneous injections in a dose of 0.5-0.7 IU/kg/week reach their genetic growth potential, resulting in a normal final height in most patients. No adverse influence of spontaneous puberty on final height was found.

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