Pubertal Development in Growth Hormone (GH)-Treated Children

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Abstract. The relationship between growth hormone (GH) secretor capacity and clinical characteristics at onset of puberty is analyzed and the prospective final height is discussed using the International Cooperative Growth Study (ICGS) database.

A total of 713 patients (464 boys and 249 girls) diagnosed as having GH deficiency of idiopathic origin by the criteria of the Foundation for Growth Science, and who entered puberty spontaneously during GH treatment, were selected from 6,058 patients treated with Genotropin in Japan.

The age at onset of puberty was significantly later in GH-treated children than in normal Japanese children. The delayed pubertal development can be attributed to a lack of the normal action of GH on the gonads. The height at onset of puberty was significantly shorter in GH-treated children than in normal children. When the change in longitudinal height velocity is compared with the normal height velocity curve by adjusting the age at onset of puberty, the mean values are distributed below the standard mean and normal adult height is unattainable. Early diagnosis and high dose GH treatment are thus important in order to allow sufficient catch-up growth before puberty, normal growth during puberty and the attainment of normal adult height.

Key words: puberty, GH deficiency, GH treatment, pubertal height gain, pubertal height velocity

Introduction

It is well known that adult height is greater in hypogonadal children and that children with untreated precocious puberty achieve shorter than normal adult height. Hence, it is speculated that pubertal develop-

ment may influence adult height. We have reported that height at onset of puberty is closely related to final height in growth hormone deficiency (GHD) (1).

It is also well known that children with idiopathic growth hormone deficiency (IGHD) develop spontaneous puberty at a later age than normal children (2-5). From evidence that GH affects gonadal function, it can be speculated that GH deficiency delays puberty.

In this study, the relation between GH secretory capacity and clinical characteristics at onset of puberty is analyzed and the prospective final height is discussed.

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Patients and Methods

The analysis is based on the ICGS database, the Japanese KIGS (Kabi International Growth Study).

A total of 713 patients (464 boys and 249 girls) diagnosed as having GH deficiency of idiopathic origin by the criteria of the Foundation for Growth Science, and who entered puberty spontaneously during GH treatment, were selected from 6,058 patients treated with Genotropin® in Japan. The patients selected were classified into three groups according to their GH secretion capacity. Complete GH deficiency (CGHD) defined by maximum peak GH response to provocation tests (except the glucagon-propranolol test) less than 5 ng/mL affected 97 patients (62 boys and 35 girls). Partial GH deficiency (PGHD) defined by maximum peak GH response to provocation tests (except the glucagon-propranolol test) less than 10 ng/mL affected 352 patients (238 boys and 114 girls). There were 264 patients (164 boys and 100 girls) with non-endocrine short stature (NESS) defined by maximum peak GH response to provocation tests (except the glucagon-propranolol test) of above 10 ng/mL. In the glucagon-propranolol

test, the cut-off points were 1.5 times the above-mentioned values.

The mean peak GH was calculated from the results of at least two provocation tests. The peak GH value by the glucagon-propranolol test was divided by 1.5 to give an adjusted mean peak GH for the purpose of comparison.

The onset of puberty was defined as the presence of a testicular volume of 4 mL or more (G2) in boys and breast development to Tanner stage 2 (B2) in girls. The age at onset of puberty was defined as the age at which these first pubertal signs were recorded in the case record forms.

Results

Clinical Variables at Start of GH Treatment and at Onset of Puberty

The age at start of GH treatment was 11.4 ± 2.1 years (mean $\pm$ SD) for boys and 10.8 ± 2.1 years for girls (Fig. 1a, 1b). Height standard deviation score (SDS) at start of GH treatment was -2.89 ± 0.83 SD for boys and -3.10 ± 0.89 SD for girls.

The age at onset of puberty was 12.7 ± 2.5 years for boys and 12.1 ± 1.7 years for girls (Fig. 2a, 2b). The mean age at onset of puberty for

Fig. 1 a, b Distribution of age at start of GH treatment in boys (a) and girls (b).

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Fig. 2a, b Distribution of age at onset of puberty in boys (a) and girls (b).

normal Japanese children is 11.5 years for boys (6) and 10.0 years for girls (7). Therefore, onset of puberty in GH-treated children was significantly later than normal both for Japanese boys and girls. Height at the onset of puberty was 135.5 ± 9.4 cm for boys and 131.6 ± 7.7 cm for girls (Fig. 3a, 3b). Since the mean height at

onset of puberty for normal Japanese boys is 144.1 cm, GH-treated boys were about 10 cm shorter than normal boys at onset of puberty. For girls, the mean height at onset of puberty was only 4.5 cm shorter than that of normal Japanese girls, *i.e.* 136.1 cm. Height SDS at the onset of puberty was -2.42 ± 0.87 SD for

Fig. 3a, b Distribution of height at onset of puberty in boys (a) and in girls (b).

Table 1 Clinical variables in three groups of boys

	CGHD	PGHD	NESS	ANOVA
Mean peak GH	2.5 ± 1.0	6.2 ± 1.5	12.7 ± 7.4	**
Start of GH treatment				
Chronological age (years)	11.41 ± 2.09	11.99 ± 2.09	11.25 ± 2.03	NS
Height (cm)	118.0 ± 16.9	121.9 ± 11.4	123.8 ± 10.9	**
Height SDS (SD)	-3.34 ± 1.16	-2.87 ± 0.69	-2.90 ± 0.81	**
Onset of puberty				
Chronological age (years)	13.44 ± 1.70	12.58 ± 1.88	12.63 ± 1.83	**
Height (cm)	138.3 ± 9.2	135.6 ± 9.4	134.4 ± 9.1	*
Height SDS (SD)	-2.56 ± 0.92	-2.30 ± 0.85	-2.54 ± 0.86	**

ANOVA: One-way analysis of variance NS: not significant *:P<0.05 **:P<0.01

boys and -2.61 ± 0.88 SD for girls. Therefore, GH treatment from the beginning of therapy to the commencement of puberty, with an average duration of 1.31 years in boys and 1.24 years in girls, resulted in a mean gain in height SDS of 0.46 SD for boys and 0.51 SD for girls.

Tables 1 and 2 compare the clinical variables for CGHD, PGHD and NESS in boys and girls. Age at the start of treatment did not differ among the three groups. Height and height SDS at the start of treatment were significantly lower in CGHD than in PGHD and NESS. Age at onset of puberty was signifi-

Table 2 Clinical variables in three groups of girls

	CGHD	PGHD	NESS	ANOVA
Mean peak GH	2.6 ± 1.2	6.3 ± 1.6	11.1 ± 5.1	**
Start of GH treatment				
Chronological age (years)	10.98 ± 2.38	10.68 ± 2.01	10.94 ± 2.06	NS
Height (cm)	113.3 ± 15.7	119.9 ± 12.1	121.3 ± 11.2	**
Height SDS (SD)	-3.56 ± 0.97	-3.06 ± 0.86	-2.98 ± 0.84	**
Onset of puberty				
Chronological age (years)	12.55 ± 2.08	11.96 ± 1.64	12.01 ± 1.83	NS
Height (cm)	132.6 ± 8.8	131.4 ± 7.4	131.4 ± 7.6	NS
Height SDS (SD)	-2.69 ± 0.82	-2.59 ± 0.85	-2.60 ± 0.93	NS

ANOVA: One-way analysis of variance NS: not significant *:P<0.05 **:P<0.01

cantly later and height and height SDS at onset of puberty were significantly lower in CGHD than in PGHD and NESS for boys. However, these differences were not observed in girls, as shown in Table 2.

Tables 3 and 4 show the correlation coefficient among the clinical variables in boys and girls. Height at onset of puberty correlated closely with age at onset of puberty. There was a significant positive correlation between the age at onset of puberty and the age at start of GH treatment, both for boys (Fig. 4a) and for girls (Fig. 4b). The earlier GH treatment was started,

Table 3 Pearson's moment correlation coefficient among clinical variables in boys (N=428)

	Start of GH treatment			Onset of puberty			Increase in height SDS
	Age	Height	Height SDS	Age	Height	Height SDS	
Start of GH treatment							
Chronological age	-0.067						
Height	0.048	0.692**					
Height SDS	0.039	-0.207**	0.383**				
Onset of puberty							
Chronological age	-0.058	0.884**	0.540**	-0.275**			
Height	-0.103*	0.690**	0.584**	0.147**	0.840**		
Height SDS	-0.066	-0.471**	-0.046	0.736**	-0.437**	0.092	
Increase in height SDS	-0.144**	-0.385**	-0.577**	-0.577**	-0.246**	-0.068	0.420**

*:P<0.05 **:P<0.01

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Table 4 Pearson's moment correlation coefficient (r) among clinical variables in girls (N=233)

	Start of GH treatment			Onset of puberty			Increase in height SDS
	Age	Height	Height SDS	Age	Height	Height SDS	
Start of GH treatment							
Chronological age	-0.031						
Height	0.081	0.750**					
Height SDS	0.139*	-0.108	0.420**				
Onset of puberty							
Chronological age	-0.090	0.892**	0.566**	-0.269**			
Height	-0.080	0.692**	0.645**	0.228**	0.774**		
Height SDS	-0.007	-0.437**	-0.034	0.720**	0.462**	0.144*	
Increase in height SDS	0.192**	-0.432**	0.613**	0.399**	0.247**	-0.118	0.349**

*,P<0.05 **P<0.01

the earlier puberty developed. The age at onset of puberty did not correlate with the duration of GH treatment. Increase in height SDS during prepuberty has a significant negative correlation with age at start of GH treatment.

The mean peak GH in CGHD and PGHD

shows a significant negative correlation with the age at onset of puberty (boys $r=-0.236$, $P<0.01$; girls $r=-0.171$, $P<0.05$).

Height Velocity

Height velocities after the onset of puberty

Fig. 4a, b Correlation between age at start of GH treatment and age at onset of puberty in boys (a) and in girls (b).

Fig. 5a, b Height velocities plotted against chronological age in boys (a) and girls (b).

are plotted against chronological age in Figs. 5a and 5b. For boys and girls, the distribution of height velocities plotted against chronological age ranges widely, but velocities tend to be higher than the standards after the age of peak height velocity, because of the delayed puberty.

Height velocity after the onset of puberty was also analyzed. The mean height velocity at 1 year, 2 years, and 3 years after onset of puberty was 6.8

cm/year, 6.7 cm/year and 5.7 cm/year, respectively, for boys and 6.3 cm/year, 4.5 cm/year, and 3.0 cm/year, respectively, for girls. When the onset of puberty is adjusted to the age when puberty normally starts, *i.e.*, 11.5 years for boys and 10.0 years for girls, the mean values show a distribution below the standard values (Fig. 6a, b).

Fig. 6a, b Height velocities plotted by adjusting the age at onset of puberty to the age when puberty normally starts in boys (a) and girls (b).

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Discussion

The age at the start of GH treatment was late. Since this survey started five years ago, only data on the older patients were selected, and therefore, the mean interval between the start of GH treatment and the onset of puberty was also short.

There is increasing evidence that GH plays an important role in gonadal function by inducing local production of insulin-like growth factor I (IGF-I) in the ovary (8) and the testis (9) and by augmenting such gonadotropin-modulated gonadal functions (10) as sex steroid production and ovulation. Thus, GH appears to affect the gonads directly. This effect is missing in GHD, which may account for the delay in pubertal development seen in this condition. The positive correlation between ages at start of GH treatment and at onset of puberty supports the hypothesis that GH is involved in gonadal function. It also suggests that the GH-associated gonadal function involved in pubertal onset is active from early childhood. The fact that in CGHD puberty commences at a later age than in PGHD and NESS, and that mean peak GH correlates negatively with age at onset of puberty in CGHD and PGHD, also supports the role of GH in gonadal function. Although GH is also known to accelerate the tempo of pubertal maturation in female Rhesus monkeys (11), as well as in IGHD (12), a direct effect of GH on the changes in gonadotropin secretion involved in the onset of puberty is doubtful. Since patients with gigantism do not enter puberty early, we know that GH does not directly affect the hypothalamo-pituitary axis to trigger the mechanism controlling pubertal onset. However, the action of GH on the gonads can affect the normalization of

pubertal development. Therefore, instead of inducing precocious puberty, early GH treatment normalizes the timing of the onset of puberty.

The normalization of pubertal onset by GH treatment shortens the height at onset of puberty in GH-treated children and leaves them shorter than average as adults, since the catch-up growth caused by GH treatment during prepuberty is insufficient to compensate for this effect. Therefore, the age at start of GH treatment correlates positively with the height at onset of puberty, although the increase in height SDS during prepuberty correlates negatively with the age at start of GH treatment. The height at onset of puberty is much shorter in GH-treated boys than in GH-treated girls. The delay of pubertal development is greater in girls than in boys, and there is no difference among the three groups of GH-treated girls. It is speculated that shorter patients were selected from among girls than from among boys, since the height SDS at start of GH treatment was below -3 SD in girls. It is also speculated that the greater delay of puberty made the height at onset of puberty taller in girls.

When the change in longitudinal height velocity is compared with the normal height velocity curve by adjusting the age at onset of puberty, the means are distributed below the standard mean. Although the pattern is comparable to the clinical observation that peak height velocity occurs at the very beginning of puberty in girls and at mid-puberty in boys (13), it is reasonable to assume that mean total pubertal growth (the increase in height from the onset of puberty to the attainment of final adult height) in GH-treated children with spontaneous puberty does not exceed that of normal children. It is also known that the pubertal height gain is less for

children with late pubertal development than for those with early pubertal development (14). Therefore, when GH-treated children of short stature enter puberty at a late age, in addition to the fact that they entered at a shorter height than normal children, the height deficit at onset of puberty cannot be recovered during puberty, and they will remain short as adults.

In a prospective study, Stanhope *et al.* (15) attempted to increase the pubertal height gain by increasing the GH dose during puberty. However, their study shows that increasing GH doses at the onset of puberty, instead of increasing final height, accelerates the progression through puberty for children with GHD. Therefore, normalization of height at onset of puberty is essential for GH-treated children to attain a normal adult height. Early diagnosis is thus important to allow catch-up growth to generate optimal height before puberty. Although there is no evidence drawn from our analysis that early start of treatment leads to taller height at onset of puberty, the lack of evidence in our study may result from selection of older patients because of the short survey period.

Starting GH treatment early is not enough to normalize pubertal height, because the catch-up growth lasts only two or three years at the dose used in Japan, *i.e.*, 0.5 U/kg/week. Job *et al.* (16) and Ranke and Guilbaud (17) showed a significant positive correlation between dose and height velocity in the 1st year of treatment in prepubertal GHD. Lesage *et al.* (18) treated prepubertal short children without GHD, using GH at a dose of 0.3 U/kg/day (2.1 U/kg/week) for two years, and then stopped the treatment. At the end of two years of high-dose treatment, the patients had gained 19 cm in height on average

and increased their height SDS with respect to both chronological age and bone age by 1.5 SD on average. High dose treatment may therefore be effective during prepuberty to allow sufficient catch-up growth and to prevent the waning phenomenon, one possible factor contributing to the low height velocity during puberty in our study could be the relatively low dose of GH we use compared with that in European countries.

In summary, GH-treated children enter puberty at a later age than normal children, but the height at onset of puberty is much shorter and the pubertal height gain is smaller than in normal children, and therefore, normal adult height is unattainable. Early diagnosis and high dose treatment are thus important in order to allow sufficient catch-up growth before puberty and normal growth during puberty, and the attainment of normal height in adulthood.

The delayed pubertal development seen in IGHD can be attributed to the lack of the normal action of GH on the gonads and the resulting failure of gonadotropin to trigger the mechanism controlling pubertal onset. The positive correlation between the ages at the start of GH treatment and at onset of puberty suggests that the GH-associated gonadal function preparing pubertal onset is active from early childhood and that early GH treatment could normalize the timing of the onset of puberty. However, once children of short stature enter puberty, the height deficit at the onset of puberty cannot be compensated for during puberty with the present GH treatment regimen, and they remain short as adults.

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