Prediction Model of Total Pubertal Growth in Idiopathic Growth Hormone Deficiency: Analysis of Data from KIGS

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When discussing total pubertal growth, it is essential that the times of onset and completion of puberty are defined accurately. For example, Gasser and colleagues [1] studied growth curves from boys and girls and defined the onset of puberty as the nadir of growth velocity (i.e. zero growth acceleration). The end of puberty was defined as the point of minimum growth acceleration. This is in contrast to Marshall and Tanner's definition of puberty, which is based on clinical signs such as genital and breast development [2]. Marshall and Tanner found that the onset of puberty was at 11.6 years in boys and 11.2 years in girls, with a total pubertal duration of about 3 years [2], whereas Gasser et al., using growth data, showed that the onset of puberty was at 10.9 years in boys and 9.7 years in girls, with a pubertal duration of 4 years [1]. Total pubertal growth was therefore greater when assessed using the methods of Gasser et al. with a difference of 3.7 cm in boys and 9.4 cm in girls [1].

We studied 303 children from KIGS (Pharmacia International Growth Database) who had idiopathic growth hormone (GH) deficiency and a GH level of less than 10 ng/ml in response to provocative testing. Patients had received at least 5 years of GH replacement, with at least 2 years of pre-pubertal and 2 years of post-pubertal therapy.

For this study, the age at onset of puberty had to be between 10 and 17 years in boys and between 9 and 16 years in girls. The age at the end of puberty was over 16 years in boys and over 14 years in girls. Height velocity at the time of the analysis needed to be less than 2 cm/year and patients were receiving a constant dose of GH, administered as six or more injections per week.

The results are summarized in table 1. Final height was reached at about 18 years in boys and 16 years in girls. Final height in boys was 0.7 standard deviations (SD) with a total pubertal growth of 25.3 cm. In girls, the final height was –1.7 SD, with a total pubertal growth of only 16 cm. Similar results were seen in an analysis of 36 patients (24 boys, 12 girls) from the University Children's Hospital, Tübingen, Germany.

When simple linear correlations were performed on the KIGS data, total pubertal growth correlated positively with both the age at onset of puberty and with the distance from target height, expressed as SD. Total pubertal growth also correlated positively with GH dose. Thus, a prediction model was developed with four variables: distance to target height (the greater the distance to target height, the greater the growth when receiving GH); mean GH dose; age at onset of puberty (the younger the age at

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Table 1. Pubertal growth in a cohort of GH-deficient patients in KIGS

	All cases (n = 303)		Boys (n = 180)	Girls (n = 123)
	Median	90% CI		
Baseline				
Mid-parental height, SD	-0.6	-2.1, 1.1	-0.6	-0.6
Maximum GH, ng/ml	4.0	1.0, 8.7	4.0	4.0
Start of GH				
Age, years	8.7	4.0, 11.9	8.9	8.3
Height, SD	-2.7	-4.0, -1.7	-2.5	-2.9
Height, cm	–	–	117.2	108.0
GH dose, mg/kg/week	0.21	0.13, 0.29	0.21	0.20
Onset of puberty				
Age, years	12.7	10.7, 15.0	13.0	12.2
Height, SD	-1.2	-2.3, 0.1	-1.1	-1.2
Height, cm			143.4	138.0
GH dose, mg/kg/week	0.20	0.12, 0.27	0.21	0.19
Near-adult height				
Age, years	17.0	14.7, 18.7	17.7	15.9
Height, SD	-0.9	-2.3, 0.5	-0.7	-1.2
Height, cm			169.5	154.8
GH dose, mg/kg/week	0.20	0.12, 0.27	0.21	0.19
Total pubertal growth, cm	20.4	10.8, 30.7	25.3	16.3
CI = Confidence intervals.				

onset, the better the response to GH); and sex. Together, these variables accounted for 70% of the total variability in final height. For example, a boy aged 14 years at the onset of puberty and with a height deficit of -2.5 SD would be predicted to grow a further 14 cm during puberty, leading to a final height of 156 cm. According to the model, doubling the dose of GH would lead to an additional final height increase of 2.5 cm.

In conclusion, the main predictors of total pubertal growth in KIGS are the age at onset of puberty and distance to target height, as well as sex and the dose of GH,

although the contribution of the size of the dose is small. Thus, GH replacement therapy should focus on normalizing height in the pre-pubertal phase.

References

- 1 Gasser T, Kneip A, Binding A, Prader A, Molinari L: The dynamics of linear growth in distance, velocity and acceleration. *Ann Hum Biol* 1991;18:187–205.
- 2 Marshall WA, Tanner JM: Growth and physiological development during adolescence. *Annu Rev Med* 1968;19:283–300.