

Effect of Growth Hormone Treatment on Adult Height of Children With Idiopathic Short Stature

Of 121 children with idiopathic short stature (ISS) entering the study to receive GH, 80 have reached adult heights after 3.5 to 10 years of GH therapy. The children were randomly assigned to either an observational control group or to treatment (0.1 mg/kg/3x weekly). The change in adult height relative to initial predicted height achieved with GH was compared with 2 groups of normal children, including 291 children with initial height SDS >-1 and bone age (BA) ≤10 years and 37 with height SDS <-1. In addition, the change in height of the 80 was compared with the change in height in untreated ISS patients (initial height SDS <-2).

The baseline and final characteristics of the 80 are recorded in Table 1, and the height SDS ± SEM (for chronologic age [CA]) versus treatment years are recorded in Figure 1. The mean baseline height SDS for the 121 ISS children was -2.7. The mean height SDS for age in the 69 treated for 5 years increased to -1.4. The 29 children treated for 7 years reached a mean height SDS of -1.0. Mean adult height also increased in the 80 compared with their initial predicted height. Sixty-five of the 80 (81%) had an increase. The mean (± SD) changes in heights from predicted heights of the treated boys and girls were 5.0 ± 5.1 cm and 5.9 ± 5.2 cm, respectively. Neither the control group of boys from the Fels Longitudinal Growth Study with basal height SDS of <-1 nor the control group of untreated ISS boys with basal height SDS <-2 reached their mean initial predicted height (mean change in height of -1.7 ± 4.2 cm and -4.2 ± 7.7 cm, respectively). Thirty-eight of 48 boys (79%) treated with GH exceeded their initial predicted adult height compared with only 2 of 11 (18%) of the untreated ISS boys. In addition, 24 of the 48 boys (50%) had a clinically important (>5 cm) increase in adult height as compared with only 1 of the 11 untreated boys. These results are summarized in Table 2 on page 24, as are the similar studies for girls.

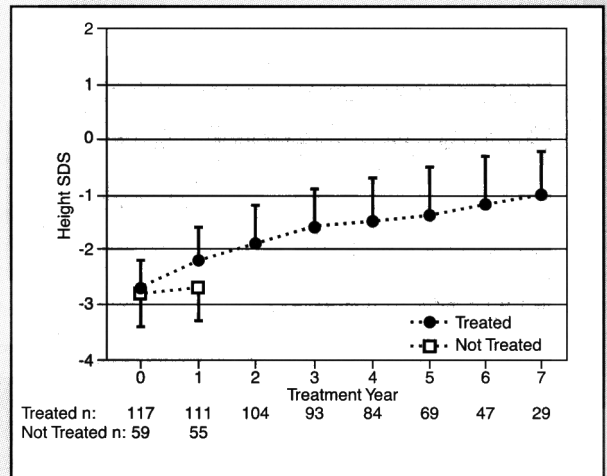
Table 1
Baseline and Final Characteristics in 80 Children With Idiopathic Short Stature Treated With Growth Hormone Until Final Height*

	Boys (n=57)	Girls (n=23)
Baseline chronologic age	10.4 ± 1.8	9.7 ± 2.1
Baseline bone age	8.7 ± 1.6	8.2 ± 1.9
Baseline height SDS	-2.8 ± -0.5	-2.7 ± 0.4
Duration of growth hormone therapy (yrs)	6.0 ± 1.7	5.5 ± 1.7
Final height (cm)	165.5 ± 7.2	153.1 ± 4.8
Pretreatment predicted adult height (cm)	160.6 ± 6.4	147.2 ± 5.1
Final height minus pretreatment PAH (cm)	5.0 ± 5.1	5.9 ± 5.2
Midparental target height (cm)	170.7 ± 4.5 (n=54)	159.0 ± 3.4
Chronologic age at final height (yrs)	18.1 ± 1.6	17.2 ± 2.0

*Values are given as means ± SD.

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Figure 1
ISS Treated With GH: Height SDS ± SEM for Chronologic Age Versus Treatment Year for Treated and Untreated Controls



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Since approximately one half of ISS children treated with GH had a >5-cm increase in adult height, as compared with initial predicted height, an important question must be addressed: Is prediction of the end result possible? In this respect, no relationship was found between the increase in adult height and the CA, BA, height age, predicted adult height, peak GH response, 12- or 24-hour integrated GH levels, or any of the insulin-like growth factor-related peptides at initiation of therapy. There also was no correlation of ultimate gain with the growth response in the first 12 or 24 months of GH treatment or the total length of treatment.

After a cogent discussion of the variability of responses and the ethics of treating ISS children, the authors concluded:

If there were no long-term benefit of treatment with GH in ISS, there would be no reason to treat and thus no ethical problem. However, our study demonstrates that there is a significant potential benefit of GH treatment. Thus the decision to treat must involve a difficult judgment of relative benefits, risks, and the cost of treatment.

Hintz RL, et al. *N Engl J Med* 1999;340:502-507.

Editor's comment: Much has been written in the literature regarding the possible treatment of ISS with GH. Many articles, both pro and con, regarding this have been abstracted in *GROWTH, Genetics, & Hormones* (Vol 11[4]:8; Vol 12[1]:14; Vol 15[1]:7-8). The study by Hintz et al abstracted here is as close to a definitive study that has been done. Each interested reader of this abstract should review the entire article in the *New England Journal of Medicine* and possibly others before deciding whether in his/her opinion GH treatment is justifiable. As for myself, I judge each instance on the characteristics and merits of the case and cost.

Fortunately, the creation of the Genentech Foundation for Growth and Development has made it possible for several psychological studies to be initiated. These will be reported subsequently regarding the psychological importance of a possible modest gain in height among such patients as reported here. Unfortunately, these studies will not be reported for another 2 to 3 years.

Robert M. Blizzard, MD

2nd Editor's comment: This interesting report provides very good data regarding the use of GH for the treatment of children with ISS. Although these children showed an increase in final adult height, they did not exhibit a major improvement even after 10 years of GH therapy. The advantage of 2 or 3 inches gain in final height has to be correlated with the cost and the long-term duration of treatment needed to achieve such a modest gain. However, we now have clear data to present and to discuss with those patients and their families when evaluating the need for GH treatment.

Fima Lifshitz, MD

Table 2
Change in Final Height in ISS Treated With GH Compared With the Change in 2 Untreated Control Groups (cm)

	Boys	Girls
	Mean (95% CI)	
△Ht: ISS treated with GH (48 boys, 21 girls)	5.0 (3.6 to 6.3)	5.9 (3.7 to 8.1)
△Ht: ISS treated with GH minus △Ht: controls (Ht SDS <-1)	6.7 (3.7 to 9.6)	2.3 (-0.6 to 5.1)
△Ht: ISS treated with GH minus △Ht: controls (Ht SDS <-2)	9.2 (5.5 to 12.8)	5.7 (2.1 to 9.4)
Ht = height △Ht = final height minus initial predicted adult height		

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A Study of Females With Deletions of the Short Arm of the X Chromosome

A clinical and molecular study of 25 females with deletions of the short arm of the X chromosome was undertaken. The deletion breakpoints, the parental origin, and the activation status of the deleted X chromosomes were determined.

The short stature observed in Turner syndrome (TS) and in patients with terminal Xp deletions results from the deletion of a homeobox gene, *SHOX*, which escapes X-inactivation and is located in the pseudoautosomal region of Xp. In determining parental origin of the X chromosome with deletions, the paternal X chromosome was defective in the vast majority. Parental disomy of the X chromosomes was excluded in 24 of the 25 deleted X chromosomes.

In all cases where the breakpoint was in or proximal to Xp22.1, the deleted X was late replicating in all cells observed.

Of the 25 patients, 23 had short stature resulting from the deletion of the *SHOX* gene in the pseudoautosomal region of Xp. None of the patients in this study had a webbed neck, which is lymphomatous in origin, although 49% of 45,X individuals in a recent review (Ogata and Matsuo. *Human Genetics* 1995;95:607-629) had neck webbing. The studies suggest that a gene (or genes) responsible may reside on Xq or very proximal on Xp. Six of 18 patients examined were found to have a low hairline posteriorly. The most distal breakpoint in such a patient was Xp22.31. Congenital edema of the extremities was described in 2 cases with breakpoints in Xp22.3 but not in any of the other cases, even when breakpoints occurred in the very proximal part of Xp. None of the patients with breakpoints distal to Xp11 had any cardiovascular problems; however, breakpoints in or proximal to Xp11 were sometimes associated with aortic valve abnormalities.

The authors concluded that the apparently normal ovarian function seen in 2 cases of females with a single copy of the *DFFRX* gene suggests that the ovarian failure seen in cases of 45,X TS may result from a mechanism other than haploinsufficiency of *DFFRX*. The absence of neck webbing in any of the patients studied suggests that the gene for this feature may lie on Xq or very proximal Xp. There were no consensus breakpoints for the other stigmata associated with lymphatic abnormalities, skeletal abnormalities, or cardiac and renal abnormalities. The presence of excess melanocytic nevi is associated with breakpoints proximal to Xp22. There is some evidence for the presence of a gene for some of the soft features of TS, located in Xp22.3, and subject to X-inactivation. In cases of distal terminal deletions, the deleted X may remain active in a proportion of cells, resulting in a Turner-like phenotype, dependent on the degree of mosaicism and the tissue specificity.

James RS, et al. *Hum Genet* 1998;102:507-516.

Editor's comment: This presentation of a very detailed clinical and cytogenetic study contributes significantly to a better understanding of the locations of the genes on the X chromosome. We have come a long way since Ferguson-Smith determined in 1965 that deletions of the whole short arm of the X chromosome in females are associated with short stature, gonadal dysgenesis, and the classic stigmata of TS. However, 34 years have passed since then. With our ever-advancing technology, probably we will know the complete genome in the next decade. We then will understand many more intricacies of gene interaction, and the time interval to learn all this will be short.

Robert M. Blizzard, MD