

## Final Height of Short Subjects of Low Birth Weight With and Without Growth Hormone Treatment

Zucchini et al report on their analyses of final heights in 2 groups of short children who were below the 10th percentile for weight. The 49 subjects presented at approximately 10 to 11 years of age. Thirty-five were below the 3rd percentile for height and 15 were between the 3rd and 10th percentiles for height. The latter were growing <3 cm/y. All had predicted heights lower than target heights, which were defined as sex-corrected midparental height (father's + mother's height) ÷ 2 + 6.5 cm for males and - 6.5 cm for females, expressed in SDS units. Each subject underwent 2 tests for GH release, arginine and levodopa stimulation. Those (29) with a peak of <8 µg/L were classified as GH deficient (GHD) and treated with

above their target height. In the untreated group, the height for CA SDS at diagnosis was the largest contributor to the variance in final height, followed by CA at diagnosis. In the treated group, height for BA SDS was followed by height for CA SDS and then CA at diagnosis, in respect to contributing variance. The Figure below graphically displays the lack of effect on the statistics of the 2 groups.

The authors state that their study confirms a negative prognosis for adult height when postnatal short stature persists, and that short subjects with low birth size will not reach their target height regardless of treatment with GH. They compare their data to that of Coutant and colleagues (*J Clin Endocrinol Metab* 1998;83:1070), who used lower doses of GH (0.4 U or 0.13 mg/kg/wk/ m<sup>2</sup> for a child) in 70 intrauterine growth retarded (IUGR) children with alleged GHD (not supported with retesting as adults) and compared the resultant data with an untreated comparable group. Final heights were comparable in both groups. Treatment was associated with a suggestive height gain of about 3.4 cm. The authors concluded that GH at this dosage level in IUGR GHD-classified patients had a limited effect on the final height of short children born with IUGR. Only those children starting treatment from a greater height for CA, and BA, and those with shorter parents had a chance of becoming taller than their parents in this study.

Zucchini S, et al. *Arch Dis Child* 2001;84:340-343.

**Editor's comment:** This interesting study confirms the clinical observations of many pediatric endocrinologists, ie, most

Table  
Results in the 2 Groups of  
Subjects Studied

	Final Height	Target Height- Final Height	Cases With Final Height> Target Height
Untreated group (n=20)	-1.87 (0.21)	0.65 (0.20)	6/20 (30%)
Males (n=9)	-1.81 (0.31)	0.56 (0.30)	3/9 (33%)
Females (n=11)	-1.92 (0.30)	0.75*(-0.33 + 1.35)	3/11 (27%)
Treated group (n=9)	-1.78 (0.18)	0.61 (0.18)	7/29 (24%)
Males (n=16)	-1.77 (0.25)	0.63 (0.27)	4/16 (25%)
Females (n=13)	-1.80 (0.25)	0.83*(0.07 + 1.20)	3/13 (23%)

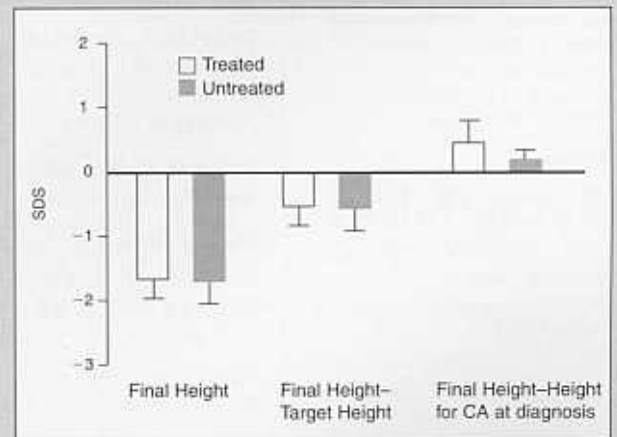
In the first 2 columns data are expressed in SDS as mean (SEM) or median\* (interquartile range).

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GH 20 U (~7 mg/m<sup>2</sup>/wk), which at the average weight per m<sup>2</sup> equals 28k. On the average, such a child has a height age of 8 years. Therefore, for this size child, administration of 0.25 mg/kg/wk of GH is slightly less than the usual dose of 0.3 mg/kg/wk given in the United States to GHD patients. Treatment ranged from 36 to 84 months, with a median of 55.7 months. Final height was determined when growth was less than 0.5 cm in the last 6 months of GH treatment or at a chronologic age (CA) greater than 16 years (females) or 18 years (males). All subjects went through puberty spontaneously and had completed pubertal development by the end of the study.

Both groups were similar at the initiation of the study with regard to birth weight, CA, height for CA SDS, height for bone age (BA) SDS, predicted height SDS, and target height SDS. Unfortunately, there was no statistical difference between the 2 groups when final height was measured (Table). Final height was significantly lower than the target height in both groups, and fewer than one third of the subjects reached a final height

Figure  
Lack of Effect in the  
2 Groups of Subjects Studied



Final height, final height-target height, and final height-height for CA at diagnosis in untreated and treated subjects.

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children with IUGR do not grow well even when given GH. Although the current study was in part retrospective, in that the physicians did not examine the children at the time of birth, they were able to determine that none of the children had any syndromes associated with short stature. The strength of the study is that it is one of the first to examine final height in these children. However, before placing undue credence on the findings, it should be noted that the children in both groups were relatively old (~10.8 years) when they presented for evaluation, and, therefore, there was little time for GH treatment prior to the onset of puberty. Despite these drawbacks, this relatively large study with final heights provides important information for physicians trying to determine whether to treat similar children with GH.

William L. Clarke, MD

**Second editor's comment:** Although substantial data indicate that administration of rhGH increases growth rate and height in short children and adolescents with IUGR selected on the basis of low birth weight or short birth length,<sup>1</sup> there are few data concerning the adult height of such subjects.<sup>2</sup> (The term "near adult" height rather than "final" height is preferred by this commentator as the latter conjures up a vision of the ultimate "finality.") Sas et al<sup>3</sup> note that administration of rhGH over 6 years to children with IUGR (birth length <3rd percentile) has no apparent deleterious effect upon glucose disposal, although fasting insulin and glucose concentrations, the insulin:glucose

ratio, and the insulin secretory response to oral glucose increased. Given the increasing evidence that impaired insulin sensitivity in subjects with IUGR untreated with rhGH may have possible long-term adverse consequences (hypertension, hypertriglyceridemia, ischemic heart disease, impaired glucose tolerance<sup>4</sup>), augmenting this potential problem with rhGH is an area of concern. Lastly, present data demonstrate once more (as if further evidence is necessary) the fallibility of provocative tests and the arbitrariness of GH concentrations in the assessment of GH secretory status in the absence of known anatomic, infectious, radiation, or neoplastic insults to the hypothalamic-pituitary axis.

Allen W. Root, MD

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2. Ranke MB, Lindberg A. Growth hormone treatment of short children born small for gestational age or with Silver-Russell syndrome: results from KIGS (Kabi International Growth Study), including the first report on final height. *Acta Paediatr* 1996;417(suppl):18-226.
3. Sas T, et al. Carbohydrate metabolism during long-term growth hormone treatment in children with short stature born small for gestational age. *Clin Endocrinol* 2001;54:243-251.
4. Botero D, Lifshitz F. Intrauterine growth retardation and long-term effects on growth. *Curr Opin Pediatr* 1999;11:340-347.

## Short Stature in Noonan Syndrome: Response to Growth Hormone Therapy

Noonan syndrome is a common syndrome occurring in both males and females; prevalence is approximately 1:1000. The gene for Noonan syndrome is found on chromosome 12p. Eighty-three percent of affected children in one series had short stature. Birth weight is usually normal but growth falls off before puberty, which is delayed. Final height is often compromised; mean adult height for males is 162.5 cm and for females 152.7 cm. There is no evidence of GH deficiency. Cardiac anomalies are frequent.

Kirk et al report on change in height SDS of 66 patients (54 males, 12 females) with Noonan syndrome, of whom 10 were treated with GH for up to 6 years. Seventy-eight percent of the subjects had a cardiac malformation, and 67% of the males suffered from cryptorchidism. The assessment of anterior pituitary function in 55 patients demonstrated normal GH secretion in all. Children with Noonan syndrome in one series had a height SDS of -2.9 compared with the normal population. The mean age at initiation of treatment was 10.2 years ( $\pm 3.3$ ). Seven of the 66 were experiencing pubertal development. The mean dose of GH was 0.79 U/kg/wk. Therapy with GH induced a significant increase in linear growth the first year, with subsequent falloff by the 4th year so that there was pretreatment growth velocity from year 4 on. The height SDS increased from -2.9 at the start of therapy to -2.3 after 6 years. The final height data were available only for 10 patients who were treated to near final height. The mean

final height was 147.2 cm in girls and 159.9 cm in boys. These results are not greater than the average height of girls and boys with Noonan syndrome who are not treated with GH.

The authors note that information on long-term therapy is often limited to small numbers of patients in other studies. The National Cooperative Growth Hormone Study in the United States has registered 150 patients treated with GH. The data in that study were similar to those in the study reported here. In the Kabi International Growth Study (KIGS) from Europe, there were 143 patients in the registry treated with GH with an increase in height SDS of 0.5 for boys and 1.1 for girls after 3 years of therapy.

The authors conclude that GH therapy for up to 6 years in a group of short patients with Noonan syndrome has been shown to increase height velocity and height SDS compared with both normal and Noonan children, although there is a waning of effect after 3 years. Only a minority of patients improved their height prediction by more than 5 cm even though treated for longer than 3 years. This is similar to the response to GH seen in patients with Turner syndrome. Further prospective studies are required to see whether GH has a long-term benefit in Noonan patients.

Kirk J, et al of the UK KIGS Executive Group on Behalf of the Participating Centers. *Arch Dis Child* 2001;84:440-443.