

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.

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**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

1. de Zegher F, et al. Growth hormone treatment of short children born small for gestational age: growth responses with continuous and discontinuous regimens over 6 years. *J Clin Endocrinol Metab* 2000;85:2816-2821.
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.

**Editor's comments:** This study is important for the data it presents on long-term GH treatment of Noonan syndrome. A recent article by MacFarlane et al (J Clin Endocrinol Metab 2001;86:1953) noted a waning of growth effect after 3 years of GH treatment. It is possible that the optimal dose of GH for Noonan syndrome has not yet been determined and that, as in

the treatment of Turner syndrome, it is a greater dose (based on kilogram of body weight) than usually prescribed for children with idiopathic GH deficiency. Unfortunately, the studies to date do not show an extremely positive response for patients with Noonan syndrome.

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## A Comparison of hGH and IGF-I as Growth-Promoting Agents in Children

Messina et al report the near adult stature of 2 children with isolated GH deficiency type 1A due to partial or complete deletion of the gene complex encoding the human GH gene cluster on chromosome 17q22-q24. In the first patient, only the gene encoding CS-B was retained; she was treated with rhGH for 12 years and achieved a near adult stature greater than her target height (153 cm vs 149 cm). This patient developed only a low titer of rhGH antibodies with low binding capacity. In the second subject, only the GH-N gene was deleted; the patient responded well to the administration of rhGH for 4 years (0.6 to 4.6 years) without development of antibodies to rhGH (height SDS increased from -5.0 to -1.4), but then abruptly developed a high titer of rhGH antibodies with high binding capacity that severely restricted the linear growth response to further rhGH administration (7.3 cm between 4.6 to 8.6 years). This child then received recombinant human insulin-like growth factor 1 (rhIGF-1) (8.6 to 13.9 years; 40 to 120 µg/kg SC twice daily); height increased only 21.2 cm during rhIGF-1 administration and the achieved near/adult height was far less than target height (128.6 cm vs 153.6 cm).

Bacckeljaaw et al describe the linear growth response to rhIGF-1 (80 to 120 µg/kg SC twice daily) in 5 children with loss-of-function mutations in the GH receptor (Laron syndrome) and 3 with deletion of the GH gene and acquired GH insensitivity due to development of high titers of antibodies to rhGH during treatment with this agent. The response to rhIGF-1 was similar in the 2 groups. Overall, the mean pretreatment height SDS was -5.6, (range, -3.4 to -7.0); after 6.5 to 7.4 years of rhIGF-1 administration, mean height SDS was -4.2 (range, -1.5 to -6.6), and only 1 child had achieved a height SDS greater than -2.0. The mean pretreatment growth rate was 4.0 cm/y and increased to 9.3 and 6.2 cm/y during the first 2 years of rhIGF-1 administration but slowed thereafter. Head circumference, weight and fat mass, spleen and kidney size, nasopharyngeal lymphoid tissue, facial soft tissues, and bone mineral density increased during treatment with rhIGF-1.

The authors of both articles concluded that the linear growth response to rhIGF-1 of GH-insensitive subjects is far less than that of GH-deficient patients to rhGH. They attribute the variation in response, in part, to the different effects of GH and IGF-1 on early chondrocyte differentiation and later clonal proliferation, respectively.

Messina MF, et al. Final height in isolated GH deficiency type 1A: effects of 5-year treatment with IGF-I. *Eur J Endocrinol* 2001;144:379-383.

Bacckeljaaw PF, Underwood LE, and the GHIS Collaborative Group. Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: a clinical research center study. *J Clin Endocrinol Metab* 2001;86:1504-1510.

**Editor's comment:** It was disappointing to learn that administration of rhIGF-1 did not restore normal linear growth in children with GH insensitivity. It is now apparent that the circulating concentration of IGF-1 is not as important a determinant of linear growth as is its tissue level. In mice without hepatic IGF-1 production, serum IGF-1 concentrations are low but linear growth is normal, suggesting that it is the local synthesis of IGF-1 that is critical for cartilage proliferation and bone growth. Since serum concentrations of "free" IGF-1 are normal in the animals without hepatic IGF-1 production, they might have accounted for the normal growth of these animals. However, the present studies in humans, in whom it is likely that during treatment "free" IGF-1 values were normal if not high (as IGF-binding protein-3 levels are low in these patients), suggest that it is not circulating but tissue IGF-1 values that are of greater importance for cartilage proliferation and linear growth. It will be of interest to examine the phenotype and response to therapy of the experimental mouse with dual knock-out of the genes encoding the GH receptor and hepatic IGF-1 synthesis.

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Butler AA, LeRoith D. Minireview: tissue-specific versus generalized gene targeting of the *igf1* and *igf1r* genes and their roles in insulin-like growth factor physiology. *Endocrinology* 2001;142:1685-1688.

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