

Lack of Correlation Between Growth Hormone Provocative Test Results and Subsequent Growth Rates During Growth Hormone Therapy

Jennifer J. Bell, MD*, and Ken Dana†

ABSTRACT. *Objectives.* To determine whether there is a relationship between the peak GH level in pituitary stimulation tests and the growth rate in response to treatment with recombinant human growth hormone (GH).

Methods. We identified 24 843 patients in the National Cooperative Growth Study database who had not been treated previously with GH therapy and divided them into three groups according to the peak GH level in pituitary stimulation testing: 1) $<10 \mu\text{g/L}$ ($n = 14\ 132$); 2) $\geq 10 \mu\text{g/L}$ ($n = 7476$); and 3) no test results reported ($n = 3235$). Growth rates in each group in response to GH therapy were examined.

Results. The children in each of the groups responded to GH therapy with a vigorous increase in growth rates (means, 8.4 to 9.5 cm/y) in the first year, followed by a gradual decline and then stabilization at 1.0 to 1.9 cm/y greater than the pretreatment values. There were large overlaps in the growth rates among the groups, but the differences were significant.

The growth rates in a smaller group of children ($n = 187$) who had normal GH responses and normal growth rates before GH therapy increased similarly in the first year of therapy (to 7.7 to 9.2 cm/y), but then declined rapidly to the pretreatment values or lower.

Conclusion. Because the GH response to pituitary stimulation testing is inadequate for diagnosing GH deficiency, such testing also is inadequate for determining whether GH treatment should be prescribed in a child with short stature. In addition, the waning response to GH therapy in normally growing short children suggests that this treatment may not have a sustained benefit in these children. *Pediatrics* 1998;102:518–520; *GH therapy, GH levels, provocative tests, growth rates.*

ABBREVIATIONS. GHD, growth hormone deficiency; GH, growth hormone; NCGS, National Cooperative Growth Study; SDS, standard deviation score(s).

It has been known for some time that the results of pituitary stimulation tests to diagnose growth hormone deficiency (GHD) may not reflect the true growth hormone (GH) status of a child with growth failure.^{1,2} On the one hand, recent studies have shown that a substantial number of children with a diagnosis of GHD by such tests have normal levels of GH when retested.^{3,4} This suggests either a large number of children with transient GHD or a

large number of false-positive results from provocative testing. On the other hand, it is widely recognized that many slowly growing children who are not GH-deficient by provocative testing will grow very well when they are given a trial of GH treatment.^{5–9} This has suggested that there is a spectrum of GHD, ranging from the classic GHD in children who cannot produce or secrete GH to GHD in children who produce enough GH to have a normal response to testing but not enough to sustain a normal growth rate.¹⁰

The question is whether there is any relationship between the amount of GH that a child secretes in response to pituitary stimulation testing and how much that child will grow in response to treatment with exogenous GH. The large number of children in the National Cooperative Growth Study (NCGS) makes it possible to examine this question on a large scale.

PATIENTS AND METHODS

From the NCGS database, we selected 24 843 children who had not received previous treatment with GH before enrollment. Their peak GH responses to pituitary stimulation testing were obtained from the enrollment forms, without regard to the type of radioimmunoassay used or whether priming with sex steroids was used before the testing.

The children were divided into groups on the basis of their response to provocative testing alone. The first group consisted of those who had a peak GH response $<10 \mu\text{g/L}$, and therefore met a criterion for GHD. The second group consisted of those with a peak response $\geq 10 \mu\text{g/L}$, considered to be a normal response. The third group consisted of those in whom no stimulation test results had been reported. Any secondary diagnoses that might have affected the children's growth pattern were not considered in the grouping. Thus, children with Turner syndrome or chronic renal insufficiency, for example, could be found in each of the three groups.

We also assessed a smaller group of children ($n = 187$) who were healthy and were growing at a normal rate but were very short for their age and sex to determine whether the NCGS data could provide any insight into the efficacy of GH treatment in such children.

Standard deviation scores (SDS) for height were calculated as $(\text{height} - \text{mean height of normal persons of the same age and sex}) / (\text{SD for height of normal persons of the same age and sex})$. The height standards for normal children were those reported by the National Center for Health Statistics.^{11,12} Target heights based on parental heights and patient sex were calculated as described by Tanner¹³ and were expressed as SDS. Annualized pretreatment growth rates were calculated from the height when GH therapy was initiated (date of enrollment in the NCGS) and the pretreatment height recorded 3 to 18 months earlier. Annualized growth rates during GH therapy were calculated by using the height recorded nearest (within 3 months) the anniversary of the initiation of treatment. Mean values were compared by using Student's *t* tests. Predicted adult heights were calculated by using a modification of the Bayley-Pinneau tables.¹⁴

RESULTS

The demographics of the three groups of patients are shown in Table 1. Fifty-seven percent (14 132) of the children had a GH response $<10 \mu\text{g/L}$ and, thus, a diagnosis of GHD. The majority (69%) of these

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TABLE 1. Demographics of 24 843 NCGS Enrollees Without Previous GH Therapy

Growth hormone level <10 $\mu\text{g/L}$
<i>n</i> = 14 132 (57%)
69% Idiopathic GHD
17% Organic GHD
14% GHD plus other causes
Growth hormone level ≥ 10 $\mu\text{g/L}$
<i>n</i> = 7476 (30%)
74% Idiopathic short stature
4% Central nervous system defects
12% Turner syndrome
10% Other causes
Growth hormone level not reported
<i>n</i> = 3235 (13%)
92% Turner syndrome, chronic renal insufficiency, unclassified growth failure, other causes
8% Idiopathic short stature

children had idiopathic GHD. Seventeen percent had organic GHD, and 14% had some other cause for growth failure in addition to GHD.

Thirty percent (7476) of the children had a GH response ≥ 10 $\mu\text{g/L}$ in at least one sample. The majority (74%) of them had an unknown cause of their short stature and were classified as having idiopathic short stature; 4% had central nervous system defects, 12% Turner syndrome, and 10% other disorders that are known to cause short stature.

Thirteen percent (3235) of the children in the database had no reported provocative testing; 8% (259) of this group were classified as having idiopathic short stature.

The only significant variable among the groups was their GH status. All other features—the pretreatment growth rate, height SDS, bone age SDS, predicted height SDS, and target height SDS—did not differ significantly. Although the target heights were normal, the mean predicted adult heights of the children were below normal in all three groups.

The changes in the growth rates in response to GH therapy are shown in Table 2. The mean duration of treatment ranged from 2.7 to 3.2 years. In each group, the initial response to GH therapy was a vigorous rise in the growth rate, followed by a gradual decline and then stabilization. The mean growth rate before treatment in the group with a GH response <10 $\mu\text{g/L}$ was

4.3 cm/y; it increased to 9.5 cm/y in the first year of GH therapy and then declined to a plateau of ~ 6.2 cm/y, or 1.9 cm/y (44%) greater than the pretreatment growth rate. The group with a GH level ≥ 10 $\mu\text{g/L}$ had a mean pretreatment growth rate of 4.3 cm/y; the rate increased to 8.4 cm/y in the first year of treatment and stabilized at ~ 5.8 cm/y, or 1.5 cm/y (35%) greater than the pretreatment rate. The children without test results rose from a mean pretreatment growth rate of 4.5 cm/y to a rate of 8.9 cm/y in the first year of therapy; the rate then stabilized, with some variation, at ~ 5.5 cm/y, or 1 cm/y (22%) greater than the pretreatment growth rate.

In all groups, the mean height SDS improved with therapy, the increases ranging from 0.8 to 1.2 SDS.

There were statistically significant differences in the growth rates and changes in height SDS among the three groups in the first 3 years of therapy; no statistical comparisons were made for subsequent years. However, there were large overlaps among the groups throughout the 9 years of reported data.

With respect to the group of 187 very short children with normal growth rates, according to the guidelines of the Lawson Wilkins Pediatric Endocrine Society for the use of GH in children with short stature,¹⁵ such children could generally be divided into the following three major groups: 1) genetic short stature, ie, healthy short children with a normal GH response to pharmacologic stimuli, a normal growth rate, a normal skeletal maturation, and a predicted adult height appropriate for their midparental target height; 2) constitutional growth delay, ie, healthy short children with a normal GH response, a normal growth rate, and a predicted adult height within the range of their target height, but *with retarded skeletal maturation*; and 3) “normal” short stature, ie, healthy short children with a normal GH response, a normal growth rate, and normal skeletal maturation, but *with a predicted adult height significantly below the target height calculated on the basis of the parental heights*.

As shown in Table 3, there were 32 children in the cohort who were considered to have genetic short stature, 85 with constitutional growth delay, and 70 with “normal” short stature. The mean length of GH therapy in these children was 2.7 years, 2.5 years, and 2.3 years, respectively. Their pretreatment growth rates

TABLE 2. Growth Rates During GH Therapy

	GH <10 $\mu\text{g/L}$		GH ≥ 10 $\mu\text{g/L}$		GH Level Not Reported	
	<i>n</i>	cm/y	<i>n</i>	cm/y	<i>n</i>	cm/y
Before treatment	9491	4.3 (2.8)	5688	4.3 (2.3)	1682	4.5 (3.0)
Year 1	9163	9.5 (2.9)*	4988	8.4 (2.3)*	1727	8.9 (3.7)*
Year 2	6259	7.8 (2.2)*	3428	7.3 (1.9)*	1036	7.2 (2.4)†
Year 3	4165	6.9 (2.1)*	2457	6.7 (2.1)*	666	6.3 (2.4)*
Year 4	2657	6.5 (2.2)	1576	6.1 (2.2)	399	6.0 (2.3)
Year 5	1689	6.2 (2.2)	941	5.7 (2.0)	233	5.9 (2.2)
Year 6	1025	6.1 (2.2)	541	5.8 (2.2)	141	5.8 (2.1)
Year 7	616	6.2 (2.1)	290	6.0 (2.5)	79	5.6 (2.1)
Year 8	373	6.3 (2.4)	153	5.9 (2.2)	60	5.2 (1.9)
Year 9	186	6.2 (2.3)	52	5.8 (2.5)	27	5.5 (1.9)
Change in height SDS after 3 years	13 180	1.2 (1.1)*	7116	1.0 (0.9)*	2838	0.8 (1.0)*
Duration of GH therapy (y)	13 348	3.2 (2.2)	7157	3.1 (2.0)	2912	2.7 (2.1)

Values are mean (SD).

* $P = .0001$, all pairwise comparisons except † $P = .068$ GH ≥ 10 $\mu\text{g/L}$ vs GH level not reported. Growth rates after 3 years were not compared for statistical significance.

TABLE 3. Growth Rates During GH Therapy in Children With Short Stature

	Genetic Short Stature		Constitutional Growth Delay		"Normal" Short Stature	
	n	cm/y	n	cm/y	n	cm/y
Before treatment	32	6.7 (1.8)	85	6.4 (1.6)	70	6.5 (2.2)
Year 1	22	8.3 (1.9)	67	9.2 (1.9)	43	7.7 (2.4)
Year 2	19	6.7 (1.9)	35	8.2 (2.0)	23	6.9 (2.2)
Year 3	9	5.7 (1.7)	23	7.3 (2.1)	17	6.5 (2.4)
Year 4	7	5.4 (2.2)	11	6.5 (1.4)	7	5.2 (3.0)

Values are mean (SD).

were normal. After an initial increase in their growth rate in the first year of treatment, the mean growth rate in the children with genetic short stature returned to baseline in the second year. The growth rate in the children with constitutional growth delay returned to baseline in the fourth year of treatment. In the children with "normal" short stature, it returned to baseline in the third year of treatment.

DISCUSSION

The clinical presentation of a poorly growing child with low GH responses is very often indistinguishable from that of a poorly growing child with adequate responses. The data in this report, based on the experience in the large NCGS cohort, indicate that in addition the growth rates in both groups of children will increase by a very similar degree with GH therapy. Thus, pituitary stimulation testing is an inadequate instrument for determining whether a child is or is not GH-deficient. Regardless of the peak GH response to testing, or even whether a child is tested at all, children will grow at a greater rate if they are treated with GH. This suggests that we should explore ways to make the diagnosis of GHD with greater certainty than these tests offer. Reexamining the arbitrary value of 10 µg/L as the cutoff between deficient and normal levels of GH may be in order; a lower cutoff value may reduce the number of false-positive results.¹⁶ Another approach would be to use the levels of insulin-like growth factor I and insulin-like growth factor binding protein 3 instead, in combination with sound auxologic evidence of inadequate growth, which may better reflect the GH status of a child with growth failure.

We also sought to determine whether GH treatment would increase the growth rates in children who had 1) normal GH responses to testing, 2) no underlying condition that might affect growth, and 3) a normal growth rate. Only a few children who were growing at a normal rate before treatment were enrolled in the NCGS, and we identified 187 who met the three criteria. In these children, there was a positive initial growth response in the first year of GH treatment, but their growth rate declined subsequently to a rate equal to or less than the pretreatment rate. This contrasts to the response to treatment in children with classic GHD, who, after the initial rise and fall in their growth rate, seem to stabilize at a rate that is greater than average and exceeds their pretreatment rate by ~2 cm/y.

This waning response to GH treatment in normally growing short children has been noted by several investigators in the past.¹⁷⁻¹⁹ The numbers of such chil-

dren in this study are too small for drawing firm conclusions, but the results do suggest that in such children, GH treatment may not have a sustained benefit.

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