

# Response to Growth Hormone in Attention Deficit Hyperactivity Disorder: Effects of Methylphenidate and Pemoline Therapy

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**ABSTRACT.** *Objective.* To determine whether treatment of attention deficit hyperactivity disorder (ADHD) with methylphenidate hydrochloride or pemoline diminishes the response to growth hormone (GH) therapy in patients with idiopathic GH deficiency (IGHD) or idiopathic short stature (ISS).

*Methods.* The National Cooperative Growth Study database was used to identify patients between 3 and 20 years of age with IGHD or ISS and those within these groups who were treated with methylphenidate or pemoline for ADHD. Their growth in response to GH treatment (change in height standard deviation score [SDS]) was compared with that of patients with IGHD or ISS who were not treated for ADHD, by using a stepwise multiple regression analysis.

*Results.* In the IGHD cohort, there were 184 patients who were being treated for ADHD and 2313 who were not. In the ISS cohort there were 117 patients who were being treated for ADHD and 1283 who were not. There was a higher percentage of males being treated for ADHD in both cohorts. In the IGHD cohort, the change in height SDS was positively associated with the number of years of GH treatment, parents' heights, body mass index, and GH injection schedule, and was negatively associated with height SDS at the initiation of GH therapy, age, and maximum stimulated GH level. The use of methylphenidate or pemoline had a negative effect on the change in height SDS, but the magnitude of the effect was small. Similar effects were noted in the ISS cohort, but body mass index and the use of methylphenidate or pemoline had no effect on the change in height SDS.

*Conclusions.* Concurrent ADHD therapy is associated with a slight decrease in the change in height SDS during GH treatment in patients with IGHD but not in those with ISS. Even in IGHD, the magnitude of the effect is small and should not deter the use of such concurrent therapy. *Pediatrics* 1998;102:497–500; *attention deficit hyperactivity disorder, methylphenidate, pemoline, growth hormone, idiopathic growth hormone deficiency, idiopathic short stature.*

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ABBREVIATIONS. ADHD, attention deficit hyperactivity disorder; GH, growth hormone; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; NCGS, National Cooperative Growth Study; SDS, standard deviation score(s); BMI, body mass index.

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The treatment of attention deficit hyperactivity disorder (ADHD) with methylphenidate hydrochloride or pemoline is associated with short-term growth deceleration. Decreased appetite that leads to low weight gain has been proposed as the cause of this slow growth, and most children will have catch-up growth after treatment with these agents has been discontinued.<sup>1–4</sup> There is evidence that alterations in dopaminergic pathways have a role in the pathogenesis of ADHD.<sup>1,5</sup> Because dopaminergic pathways also are involved in the regulation of growth hormone (GH) secretion,<sup>6</sup> the association between growth failure and ADHD also may have an endocrine cause. It is also possible that medications such as methylphenidate and pemoline have direct effects on cartilage metabolism.<sup>7</sup>

We studied the effects of therapy with methylphenidate or pemoline on growth in response to exogenous GH in patients with both ADHD and idiopathic growth hormone deficiency (IGHD) or idiopathic short stature (ISS), using a large North American database of patients treated with GH, the National Cooperative Growth Study (NCGS).

## PATIENTS AND METHODS

### Patients

The NCGS is a postmarketing database of patients in the United States and Canada who have been treated with GH products manufactured by Genentech Inc (South San Francisco, CA). The methods of patient enrollment and data collection have been described previously.<sup>8</sup> Patients in the NCGS database were included in this analysis if they met the following criteria: 1) diagnosis of IGHD or ISS as determined by the treating physician (confirmed by a maximum stimulated GH level <10 µg/L for IGHD and ≥10 µg/L for ISS); 2) no GH therapy before enrollment; 3) prepubertal at enrollment; 4) between 3 and 20 years of age at enrollment; 5) height below the 5th percentile for age and sex; 6) no other significant medical conditions that affect growth; and 7) height reported after at least 180 days of GH therapy. Patients who met the criteria above and who also were treated for ADHD with either methylphenidate or pemoline were identified. The information provided on the case report forms was used for the analysis. The GH levels were determined at laboratories chosen by the treating physician.

### Statistics

Descriptive data are reported as mean ± SD for continuous variables and as percentages for categorical variables. Height SD scores (SDS) were calculated as follows: SDS = (height – mean height of normal persons of the same age and sex)/(SD of height of normal persons of the same age and sex). Height and weight standards were obtained from data collected by the National Center for Health Statistics.<sup>9</sup> Differences in the mean values between the ADHD and comparison groups were tested by using Student's *t* tests and differences in the proportions were tested by using  $\chi^2$  tests.

The response to GH therapy was defined as the change in height SDS from the time that GH therapy was initiated to the time of the most recent height measurement or the height measurement when treatment was discontinued, whichever oc-

**TABLE 1.** Patient Characteristics

	ADHD-IGHD (n = 184)	IGHD (n = 2313)	ADHD-ISS (n = 117)	ISS (n = 1283)
Male sex, number (%)	161 (88)**	1699 (73)	99 (85)*	957 (75)
Entered puberty during treatment, number (%)	87 (47)	1095 (47)	54 (46)	657 (51)
GH injected ≥4 times a week, number (%)	157 (85)	1791 (77)	94 (80)	1006 (78)
Age at enrollment, y	9.2 ± 3.0	9.1 ± 3.5	9.2 ± 2.8	9.6 ± 3.1
Height SDS	-2.8 ± 0.7**	-3.0 ± 0.9	-2.8 ± 0.7	-2.9 ± 0.7
Maximum stimulated GH level, µg/L	5.9 ± 2.4**	5.6 ± 2.7	16.1 ± 5.8	17.7 ± 9.5
BMI (kg/m <sup>2</sup> )	15.7 ± 2.1***	16.5 ± 2.9	15.4 ± 1.6**	15.9 ± 2.0
Bone age deficit, y	2.0 ± 1.0*	2.2 ± 1.3	2.0 ± 1.1	2.2 ± 1.3
Maternal height SDS	-0.7 ± 1.2	-0.8 ± 1.3	-1.0 ± 1.7	-1.1 ± 1.2
Paternal height SDS	-0.3 ± 1.2	-0.5 ± 1.2	-0.5 ± 1.3*	-0.7 ± 1.3
Years of GH therapy	3.0 ± 2.0	2.7 ± 1.8	2.8 ± 1.9	2.7 ± 1.8
Change in height SDS	1.2 ± 0.8**	1.3 ± 0.9	1.0 ± 0.7	1.1 ± 0.7

\* *P* < .05; \*\* *P* < .01; \*\*\* *P* < .001.

Comparisons are between ADHD-IGHD and IGHD or between ADHD-ISS and ISS, as appropriate.

curred first. This definition of response (as opposed to yearly growth rates) avoids problems associated with annualizing growth data for intervals different from 12 months and makes it possible to use data from all patients (including dropouts) in the analysis, thereby eliminating concerns about possible patient-selection bias. Multiple stepwise regression analysis was used for determining the relative influence of the following variables on the change in height SDS: age at enrollment, sex, height SDS at enrollment, body mass index (BMI), mother’s height SDS, father’s height SDS, maximum stimulated GH level, frequency of GH injections, onset of puberty during therapy, and methylphenidate or pemoline therapy.

A result was considered statistically significant if the *P* value was < .05. All statistical analyses were performed by using the Statistical Analysis System (SAS version 6.11, SAS Institute Inc, Cary, NC).

**RESULTS**

We identified a total of 3897 patients who met the entry criteria, 301 of whom also had been treated with methylphenidate or pemoline for ADHD. The comparison groups consisted of 184 patients with ADHD and IGHD and 2313 patients with IGHD and of 117 patients with ADHD and ISS and 1283 patients with ISS.

**TABLE 2.** Factors With a Significant Effect on the Response to GH Therapy

	Regression Coefficient	Contribution to R <sup>2</sup>	<i>P</i>
IGHD (model R <sup>2</sup> = .510)			
Duration of GH therapy	0.24	.318	<.001
Paternal height SDS	0.06	.009	<.001
Maternal height SDS	0.06	.005	<.001
BMI (log)	0.45	.005	<.001
Height SDS at enrollment	-0.26	.084	<.001
Age at enrollment	-0.07	.041	<.001
Maximum stimulated GH level (log)	-0.17	.026	<.001
GH injected ≤3 times a week	-0.33	.020	<.001
Treatment with methylphenidate or pemoline	-0.17	.002	.001
ISS (model R <sup>2</sup> = .447)			
Duration of GH therapy	0.21	.367	<.001
Maternal height SDS	0.05	.010	<.001
Paternal height SDS	0.04	.005	<.001
Age at enrollment	-0.04	.033	<.001
Height SDS at enrollment	-0.15	.015	<.001
GH injected ≤3 times a week	-0.19	.013	<.001
Maximum stimulated GH level (log)	-0.11	.004	.002

**Enrollment Characteristics**

Enrollment characteristics of the groups are shown in Table 1.

*IGHD Cohort*

There were small but significant differences between the ADHD-IGHD group and the IGHD group in several variables that have been shown to predict the response to GH therapy. These were height SDS at enrollment (-2.8 ± 0.7 vs -3.0 ± 0.9; *P* < .01), maximum stimulated GH level (5.9 ± 2.4 vs 5.6 ± 2.7 µg/L; *P* < .01); BMI (15.7 ± 2.1 vs 16.5 ± 2.9 kg/m<sup>2</sup>; *P* < .001), and GH injection schedule (cumulative weighted average ≥4 times a week, 85% vs 77%; *P* < .05). Other predictive variables, including age at enrollment, parental heights, and weekly GH dose, that have been shown previously to be important were not different between the two groups. Male sex was preponderant in both groups and was significantly greater in the ADHD-IGHD group (88% vs 73%; *P* < .01). The bone age deficit was significantly less in the ADHD-IGHD group (2.2 ± 1.3 vs 2.0 ± 1.0 years; *P* < .05). Sex and bone age deficit, however, have not had important predictive power in other analyses of the response to GH therapy.<sup>10</sup>

*ISS Cohort*

There were fewer significant differences between the ADHD-ISS and ISS groups. These were male preponderance (85% vs 75%; *P* < .05), BMI (15.4 ± 1.6 vs 15.9 ± 2.0 kg/m<sup>2</sup>; *P* < .01), and father’s height SDS (-0.5 ± 1.3 vs -0.7 ± 1.3; *P* < .05). All other variables, eg, height SDS, age at enrollment, age at onset of puberty, GH injection schedule, bone age deficit, and mother’s height SDS, were similar between the two groups.

**Response to GH**

The factors that had a significant effect on the response to GH therapy are shown in Table 2.

*IGHD Cohort*

The change in height SDS was positively associated with (in order of decreasing predictive importance) duration of GH therapy, GH injection schedule, father’s height SDS, mother’s height SDS, and

BMI. It was negatively associated with height SDS and age at NCGS enrollment and maximum stimulated GH level. Sex and change in pubertal status during GH therapy did not affect the change in height SDS. Treatment with methylphenidate or pemoline had a negative effect on the change in height SDS, but the magnitude of the effect was small and the magnitude of the difference in the change in height SDS between the ADHD-IGHD and the IGHD groups decreased with time (Fig 1).

#### ISS Cohort

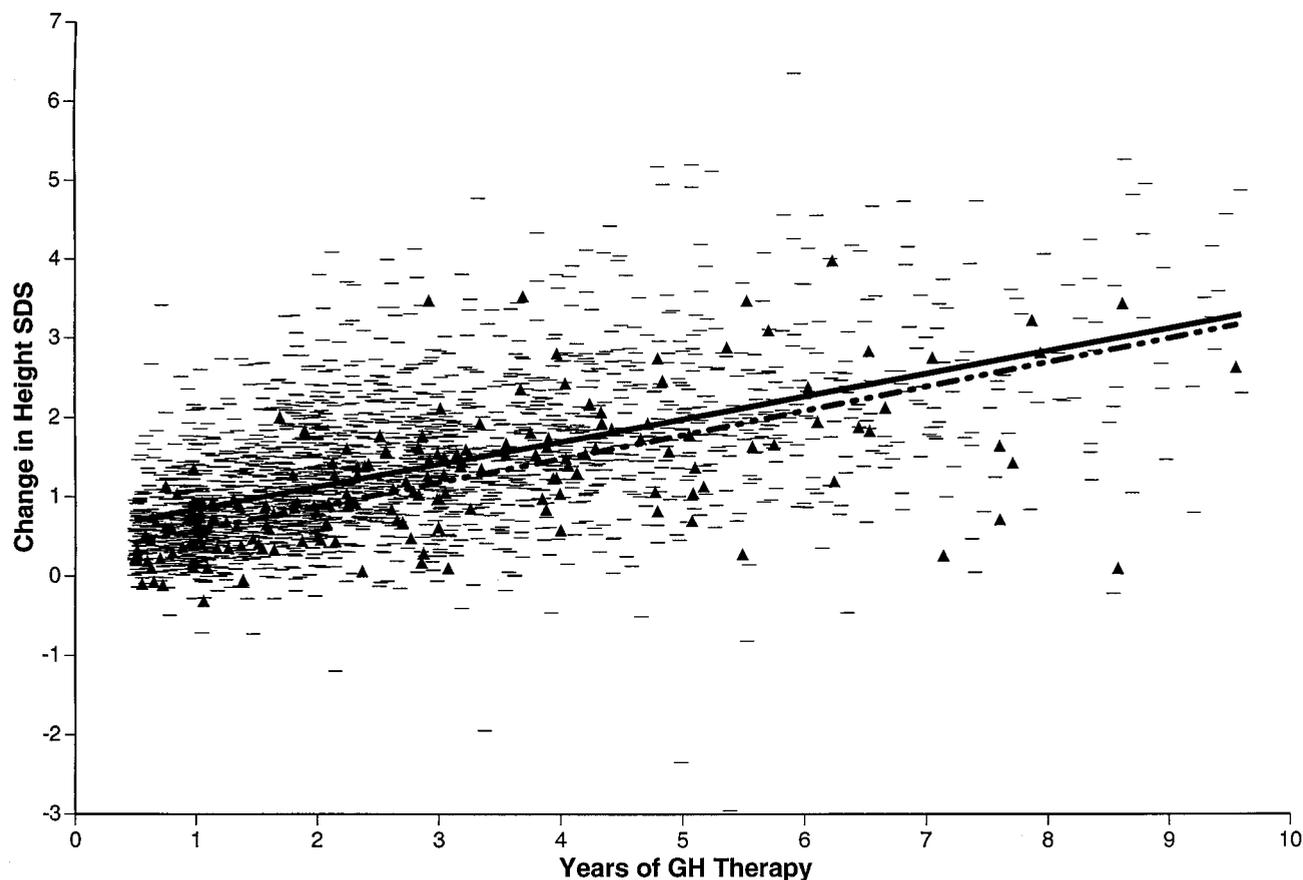
The change in height SDS was positively associated with (in order of decreasing predictive importance) duration of GH therapy, GH injection schedule, mother's height SDS, and father's height SDS. It was negatively associated with age at enrollment, height SDS, and maximum stimulated GH level. BMI, sex, and change in pubertal status during GH treatment did not affect the change in height SDS. Therapy with methylphenidate or pemoline did not have a significant negative effect on the change in height SDS (Fig 2).

### DISCUSSION

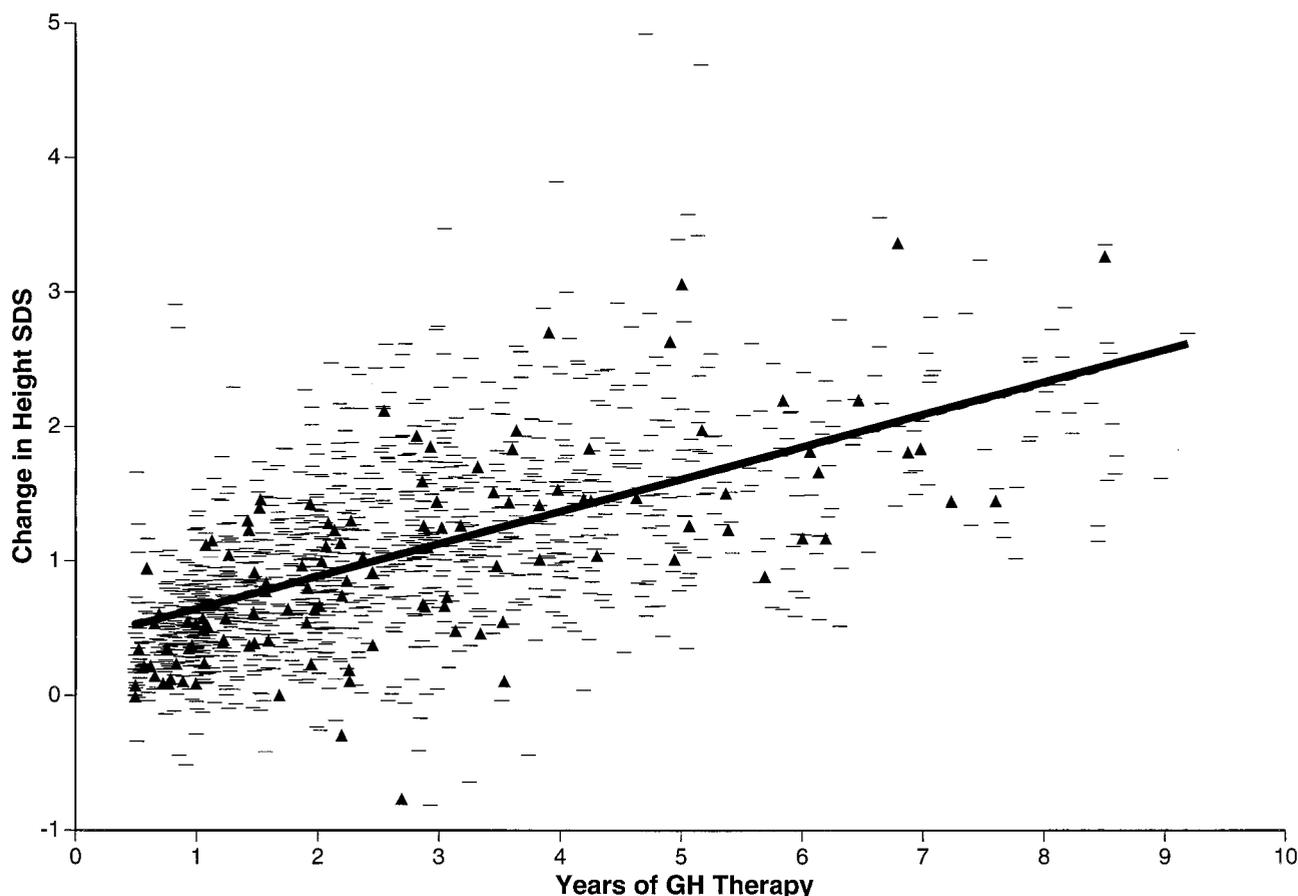
The variables shown to be important predictors of the change in height SDS in the patients with IGHD (longer duration of GH therapy, height SDS when GH therapy was initiated, parental heights, BMI,

degree of GH deficiency, and GH injection schedule) also have been reported as significant predictors of the growth rate during the first year of GH treatment in other studies in children with IGHD.<sup>10-16</sup> Because the patients who were treated with methylphenidate or pemoline were different from the other patients with IGHD in several variables that have been shown to predict the response to GH treatment, we used a stepwise multiple regression to determine the effect of treatment with methylphenidate or pemoline on the response to GH therapy. We found that treatment with these agents had a negative effect on the change in height SDS in the IGHD cohort but not in the ISS cohort. The magnitude of this effect in the IGHD cohort was small, contributing only  $-0.17$  SD over an average of 3 years of treatment with GH. Furthermore, examination of the slopes of the regression lines indicates that the effect may decrease with time.

Because the nature of the neurochemical changes associated with ADHD and their effects on the hypothalamic-pituitary-insulin-like growth factor I axis are not well understood,<sup>17</sup> the role, if any, of ADHD or its treatment with methylphenidate or pemoline in the short stature often associated with this disorder is not clear. By confining our study to patients with IGHD and ISS who were treated with GH, we isolated one part of the growth axis, namely,



**Fig 1.** The effect of treatment with methylphenidate or pemoline on the growth response to GH therapy in patients with IGHD, showing the regression equations for the predicted change in height SDS with GH therapy with (dot-dash line) and without (solid line) methylphenidate or pemoline. The individual changes in height SDS in those who were (solid triangles) and those who were not (dashes) treated with methylphenidate or pemoline are also shown.



**Fig 2.** The effect of treatment with methylphenidate or pemoline on the growth response to GH therapy in patients with ISS, showing identical regression equations for the predicted change in height SDS with GH therapy with (dot-dash line) and without (solid line) methylphenidate or pemoline. The individual changes in height SDS in those who were (solid triangles) and those who were not (dashes) treated with methylphenidate or pemoline are also shown.

the response to GH, from possible effects on the hypothalamic-pituitary axis.

From the point of view of the physician who provides care to children with ADHD, the message is clearer. Therapy with methylphenidate or pemoline has no demonstrative effect on the response to GH therapy in children with ISS. The small negative effect of these agents on the response to GH therapy in patients with IGHD should not deter clinicians from using them in children with IGHD when they are medically indicated.

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