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

Jayashree K. Rao, MD*; Joanne R. Julius, MS‡; Timothy J. Breen, PhD‡; and Sandra L. Blethen, MD, PhD‡

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.

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.

From the *Department of Pediatrics, Louisiana State University School of Medicine, New Orleans, Louisiana; and the Department of Medical Affairs, Genentech Inc, South San Francisco, California. This work was presented in part at the National Cooperative Growth Study Eleventh Annual Investigators Meeting, September 25–28, 1997, Washington, DC. Received for publication Feb 6, 1998; accepted Mar 20, 1998. Address correspondence to Jayashree K. Rao, MD, Department of Pediatrics, Louisiana State University School of Medicine, 1542 Tulane Ave, New Orleans, LA 70112. PEDIATRICS (ISSN 0031-4005). Copyright © 1998 by the American Academy of Pediatrics.
TABLE 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHD–IGHD (n = 184)</th>
<th>IGHD (n = 2313)</th>
<th>ADHD–ISS (n = 117)</th>
<th>ISS (n = 1283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, number (%)</td>
<td>161 (88)**</td>
<td>1699 (73)</td>
<td>99 (85)*</td>
<td>957 (75)</td>
</tr>
<tr>
<td>Entered puberty during treatment, number (%)</td>
<td>87 (47)</td>
<td>1095 (47)</td>
<td>54 (46)</td>
<td>657 (51)</td>
</tr>
<tr>
<td>GH injected &gt; 4 times a week, number (%)</td>
<td>157 (85)</td>
<td>1791 (77)</td>
<td>94 (80)</td>
<td>1006 (78)</td>
</tr>
<tr>
<td>Age at enrollment, y</td>
<td>9.2 ± 3.0</td>
<td>9.1 ± 3.5</td>
<td>9.2 ± 2.8</td>
<td>9.6 ± 3.1</td>
</tr>
<tr>
<td>Height SDS</td>
<td>−2.8 ± 0.7***</td>
<td>−3.0 ± 0.9</td>
<td>−2.8 ± 0.7</td>
<td>−2.9 ± 0.7</td>
</tr>
<tr>
<td>Maximum stimulated GH level, μg/L</td>
<td>5.9 ± 2.4**</td>
<td>5.6 ± 2.7</td>
<td>16.1 ± 5.8</td>
<td>17.7 ± 9.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.7 ± 2.1***</td>
<td>16.5 ± 2.9</td>
<td>15.4 ± 1.6**</td>
<td>15.9 ± 2.0</td>
</tr>
<tr>
<td>Bone age deficit, y</td>
<td>2.0 ± 1.0*</td>
<td>2.2 ± 1.3</td>
<td>2.0 ± 1.1</td>
<td>2.2 ± 1.3</td>
</tr>
<tr>
<td>Maternal height SDS</td>
<td>−0.7 ± 1.2</td>
<td>−0.8 ± 1.3</td>
<td>−1.0 ± 1.7</td>
<td>−1.1 ± 1.2</td>
</tr>
<tr>
<td>Paternal height SDS</td>
<td>−0.3 ± 1.2</td>
<td>−0.5 ± 1.2</td>
<td>−0.5 ± 1.3*</td>
<td>−0.7 ± 1.3</td>
</tr>
<tr>
<td>Years of GH therapy</td>
<td>3.0 ± 2.0</td>
<td>2.7 ± 1.8</td>
<td>2.8 ± 1.9</td>
<td>2.7 ± 1.8</td>
</tr>
<tr>
<td>Change in height SDS</td>
<td>1.2 ± 0.8**</td>
<td>1.3 ± 0.9</td>
<td>1.0 ± 0.7</td>
<td>1.1 ± 0.7</td>
</tr>
</tbody>
</table>

* P < .05; ** P < .01; *** P < .001. Comparisons are between ADHD–IGHD and IGHD or between ADHD–ISS and ISS, as appropriate.

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**

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient</th>
<th>Contribution to R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHD (model R² = .510)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of GH therapy</td>
<td>0.24</td>
<td>.318</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paternal height SDS</td>
<td>0.06</td>
<td>.009</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal height SDS</td>
<td>0.06</td>
<td>.005</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (log)</td>
<td>0.45</td>
<td>.005</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height SDS at enrollment</td>
<td>−0.26</td>
<td>.084</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at enrollment</td>
<td>−0.07</td>
<td>.041</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum stimulated GH level (log)</td>
<td>−0.17</td>
<td>.026</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GH injected ≥ 3 times a week</td>
<td>−0.33</td>
<td>.020</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment with methylphenidate or pemoline</td>
<td>−0.17</td>
<td>.002</td>
<td>.001</td>
</tr>
<tr>
<td>ISS (model R² = .447)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of GH therapy</td>
<td>0.21</td>
<td>.367</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal height SDS</td>
<td>0.05</td>
<td>.010</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paternal height SDS</td>
<td>0.04</td>
<td>.005</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at enrollment</td>
<td>−0.04</td>
<td>.033</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height SDS at enrollment</td>
<td>−0.15</td>
<td>.015</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GH injected ≥ 3 times a week</td>
<td>−0.19</td>
<td>.013</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum stimulated GH level (log)</td>
<td>−0.11</td>
<td>.004</td>
<td>.002</td>
</tr>
</tbody>
</table>

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/m²; 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.

**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/m²; 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. 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, 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,
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.

REFERENCES

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.
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