Final Adult Height in Children with Congenital Adrenal Hyperplasia Treated with Growth Hormone

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Context: Patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency typically reach a final adult height well below their mid-parental target height.

Objective: The objective of this study was to examine whether GH alone or in combination with an LHRH analog (LHRHa) improved the final adult height in patients with CAH.

Design: The study was a nonrandomized prospective study.

Setting: The study was conducted at two university hospitals in New York City, NY.

Participants: Thirty-four patients with CAH treated with GH participated in this study. Nineteen males and 15 females who were predicted to be more than 2SD below their mid-parental target height or more than 2SD below the population mean received GH until reaching final adult height. In addition to GH, 27 patients (16 males, 11 females) were also treated with an LHRHa.

Intervention: The mean duration of GH treatment was 5.6±1.8 yr in males and 4.5±1.6 yr in females. The mean duration of LHRHa therapy was 3.7±1.7 yr for both sexes.

Main Outcome Measures: The primary endpoint variables were final adult height, final height discrepancy, and gain in height.

Results: Males reached a significantly higher final adult height (172.0±4.8 cm) than their initial predicted height (162.8±7.7 cm) (P<0.00001). Females also reached a significantly higher final adult height (162.2±5.3 cm) than initially predicted (151.7±5.2 cm) (P<0.0000001). Mean gain in height was 9.2±6.7 cm in males and 10.5±3.7 cm in females.

Conclusion: Our results indicate that GH alone or in combination with LHRHa improves final adult height in patients with CAH. (J Clin Endocrinol Metab 96: 1710–1717, 2011)

Patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) often reach a final adult height significantly below their parentally determined target height (1–3). As a result of excess androgens, which do not require 21-OHD for synthesis (4), affected children frequently develop rapid linear growth during childhood along with premature epiphyseal fusion (5), thereby compromising their adult height (6–12).

Previous studies have demonstrated that the adult height reached by patients with CAH is generally well below the mid-parental target height and that the degree of hormonal control does not necessarily correlate with the degree of short stature (7, 8, 13–26). In a metaanalysis of 18 studies published between 1977 and 1997, the overall mean weighted final height compared with mid-parental target height was −1.57 SD for males and −1.24 SD for females (27). Another recent metaanalysis of 35 studies...
published between 1977 and 2008 reported an overall mean final height SD score (SDS) of −1.38 (−1.56 to −1.20) and a corrected height SDS relative to mid-parental target height of −1.03 (−1.20 to −0.86) (28).

There are several factors contributing to the failure to achieve optimal adult height in patients with CAH. Excess adrenal androgens result in accelerated linear growth, accompanied by premature fusion of the epiphyses, ultimately compromising adult stature. Additionally, central precocious puberty may develop in patients with CAH due to androgen activation of the hypothalamic-pituitary-gonadal axis, thus exacerbating premature epiphyseal fusion (29, 30). Finally, the treatment of CAH with chronic glucocorticoid therapy, even at replacement doses, has been associated with poor growth (31), and long-term glucocorticoid treatment during childhood, particularly during the pubertal growth spurt, can compromise final height (32–34).

For CAH patients who develop central precocious puberty, LHRH analog (LHRHa) can effectively suppress puberty. However, treatment with LHRHa often results in a subsequent deceleration of growth velocity (35) and is unlikely by itself to have a significant impact on adult height. The administration of GH, on the other hand, has been demonstrated to counter the growth-suppressing effects of glucocorticoids and LHRHa (36) and could thus be useful in improving adult height. Others have shown that the combination of GH and LHRHa is effective in improving height prediction and final height in non-CAH children with central precocious puberty (37–39).

Our group has previously reported a significant improvement in the 2-yr height prediction (16) and final adult height in 14 patients with CAH treated with GH (40). We now report the effect of GH alone or in combination with LHRHa on final adult height in 34 patients with CAH.

**Subjects and Methods**

**Subjects**

The study was a nonrandomized study. All patients who were eligible for the study were offered entry. The treatment group consisted of 34 patients with 21-OHD CAH (documented by clinical, hormonal, and DNA evidence), who were treated with GH from 1992–2010. Inclusion criteria were 1) bone age of at least 6 yr, 2) bone age greater than 1 sd ahead of chronological age, 3) adult height prediction by the Bayley-Pinneau method (41) of at least 2 sd below mid-parental target height or at least 2 sd below the population mean (males, population mean 177 ± 7 cm; females, population mean 163 ± 6 cm), and 4) open epiphyses (bone age <13 yr in girls and <15 yr in boys). Exclusion criteria were 1) closed epiphyses, 2) medical disorder or treatment with medications other than hydrocortisone known to impair growth, or 3) noncompliance with medical treatment for CAH.

**Study design**

The institutional review boards at Weill Medical College of Cornell and Mount Sinai School of Medicine approved the study, and informed assent and consent were obtained from each subject and his/her parent or guardian. Upon enrollment and every 3 months, each subject was evaluated for height, weight, pubertal status, and adrenal hormones. Height was recorded to the nearest 0.1 cm as the average of three measurements using a Harpenden stadiometer. Mid-parental target height was calculated according to the method of Tanner et al. (24). Bone age was determined annually according to the method of Greulich and Pyle (42). Predicted adult height was calculated using bone age and height according to the Bayley-Pinneau method (41). Height discrepancy was calculated as predicted height minus target height. Final height discrepancy was calculated as final adult height minus target height. Gain in height was defined as final adult height minus predicted height.

Subjects with either precocious or early central puberty (<11 yr in males or <10 yr in females) were offered treatment with LHRHa in addition to GH. The decision to treat with LHRHa was made independently of the study.

All subjects received recombinant human GH [somatropin (ribosomal DNA origin)] at an initial dose of 0.3 mg/kg per week divided into seven sc doses per week. The dose was increased as needed in 0.02-mg/kg per week increments up to a maximum dose of 0.45 mg/kg per week to maintain a growth velocity at 50th or above percentile for bone age without exceeding the normal range of IGF-I. GH treatment was continued until final adult height was reached. Final adult height was defined as a growth velocity of less than 1.5 cm/yr over a 6-month period and bone age of at least 15 yr in girls or at least 17 yr in boys. In 20 of the treated subjects, Humatrope was provided by Eli Lilly & Co. (Indianapolis, IN). The remaining 14 subjects received GH (all commercially available brands) through their insurance or through a pharmaceutical assistance program. For patients additionally treated with LHRHa, the cost of LHRHa was covered through the patients’ medical insurance plans. Lupron (leuprolide acetate) was given at a dosage of 300 μg/kg im every 28 d. LHRHa was continued until there was no longer any height discrepancy, i.e., height prediction equal or exceeded target height, as long as the child was at an appropriate chronological age for puberty. If the height discrepancy was never recovered, then LHRHa was discontinued when the growth velocity fell to less than 3 cm/yr over a 6-month period with a bone age of at least 13 yr in girls and 14 yr in boys. Blood for measurement of IGF-I, IGF-binding protein 3, thyroid function, and hemoglobin A1c was obtained annually in all subjects. Bone age was obtained annually. Each bone age was read by a single pediatric endocrinologist blinded to the subject’s identity.

All subjects received glucocorticoid therapy, the dose of which was adjusted as necessary to maintain optimal suppression of adrenal steroids. The target range for 17-hydroxyprogesterone levels (17OHP) was 200-1000 ng/dl when drawn 2 h after the morning dose of hydrocortisone. Additionally, mineralocorticoid replacement therapy in the form of fludrocortisone (0.05–0.15 mg daily) was given to patients classified with salt-wasting CAH, as determined by either a history of salt-wasting crisis or undetectable aldosterone levels. Good adrenal control
was defined as more than 75% of 17OHP levels under 1000 ng/dl. Fair adrenal control was defined as 25–75% of 17OHP levels under 1000 ng/dl. Poor control was defined as less than 25% of 17OHP levels under 1000 ng/dl.

**Statistical analysis**

The primary endpoint variables were final adult height, final height discrepancy, and gain in height. A Student’s t test was used for comparisons between two groups. A student’s paired t test was used for comparisons between time points, i.e. baseline height prediction compared with final adult height. Pearson correlation was used to measure the association between continuous variables. A result was considered statistically significant if $P < 0.05$.

**Results**

**Baseline characteristics**

Bone age at the start of GH therapy was 12.2 ± 1.7 yr in males and 10.5 ± 1.7 yr in females. Mean target height was 176.3 ± 4.8 cm in males and 162.8 ± 6.3 cm in females. Mean predicted height was 162.8 ± 7.7 cm in males and 151.7 ± 5.2 cm in females. Height discrepancy at baseline was −13.5 ± 7.7 cm in males and −11.1 ± 4.8 cm in females (Table 1).

**Final adult height**

Final adult height was significantly higher than baseline predicted height in both males (172.0 ± 4.8 cm vs. 162.8 ± 7.7 cm, $P < 0.00001$) and females (162.2 ± 5.3 cm vs. 151.7 ± 5.2 cm, $P < 0.000001$) (Table 2 and Fig. 1).

The final height discrepancy compared with baseline height discrepancy was significantly reduced in both males (−4.3 ± 4.6 cm vs. −13.5 ± 7.7 cm, $P < 0.00001$) and females (−0.6 ± 3.2 cm vs. −11.1 ± 4.8 cm, $P < 0.000001$). Mean gain in height was 9.2 ± 6.7 cm for males and 10.5 ± 3.7 cm for females.

There was no statistical difference between males and females regarding duration of GH, final height SDS, or gain in height. However, final height discrepancy was significantly better in females (−0.6 ± 3.2 cm) than in males (−4.3 ± 4.6 cm) ($P < 0.01$) (Table 3).

**Duration of GH therapy**

Mean age at the start of GH therapy was 8.8 ± 2.5 yr in males and 8.4 ± 1.9 yr in females. The mean age at completion of GH treatment in males was 14.3 ± 1.4 yr and in females was 12.9 ± 1.6 yr. The mean duration of GH treatment was 5.6 ± 1.8 yr in males and 4.5 ± 1.6 yr in females. There was a significant negative correlation between gain in height and age at the start of GH ($r = −0.58; P < 0.001$). There was also a significant correlation between gain in height and duration of GH treatment ($r = 0.46; P < 0.01$).

**Treatment with or without LHRHa**

The mean age at initiation of LHRHa therapy was 9.6 ± 1.7 yr, and the mean age at completion of LHRHa

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**TABLE 1.** Baseline characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 19)</th>
<th>Female (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age (yr)</td>
<td>8.8 (2.5)</td>
<td>8.4 (1.9)</td>
</tr>
<tr>
<td>Bone age (yr)</td>
<td>12.2 (1.7)</td>
<td>10.5 (1.7)</td>
</tr>
<tr>
<td>Target height (cm)</td>
<td>176.3 (4.8)</td>
<td>162.8 (6.3)</td>
</tr>
<tr>
<td>Predicted height (cm)$^a$</td>
<td>162.8 (7.7)</td>
<td>151.7 (5.2)</td>
</tr>
<tr>
<td>Height discrepancy (cm)</td>
<td>−13.5 (7.7)</td>
<td>−11.1 (4.8)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD). Height discrepancy = predicted height − target height. NS, Not significant; SV, simple-virilizing CAH; SW, salt-wasting CAH.

$^a$ Predicted height based on Bayley-Pinneau method for accelerated bone age.

**TABLE 2.** Final adult height (predicted compared with final)

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Final</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n = 19)</td>
<td>162.8 (7.7)</td>
<td>172.0 (4.8)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Female (n = 15)</td>
<td>151.7 (5.2)</td>
<td>162.2 (5.3)</td>
<td>&lt;0.000001</td>
</tr>
</tbody>
</table>

Data are expressed as mean (sd).
therapy was 13.3 ± 1.1 yr. The mean duration of LHRHα therapy was 3.7 ± 1.7 yr. There was not a significant correlation between gain in height and duration of LHRHα treatment. There was a significant negative correlation between gain in height and age at the start of LHRHα (r = −0.39; P < 0.05).

The mean gain in height was not significantly different between subjects treated with GH plus LHRHα (9.2 ± 5.8 cm) and those treated with GH alone (11.8 ± 4.0 cm). There was also no significant difference in final height SDS or duration of GH treatment between the two groups. Subjects treated with GH plus LHRHα, however, started GH therapy at a later age compared with subjects treated with GH alone (8.9 ± 2.2 vs. 7.4 ± 2.0 yr, P < 0.05). They also started GH with a more advanced bone age than those not treated with LHRHα (11.8 ± 1.6 vs. 9.9 ± 2.3 yr, P < 0.05) (Table 4).

### Classical vs. nonclassical patients

Final height SDS was higher in nonclassical patients than in classical patients (0.07 ± 0.5 vs. −0.51 ± 0.9, P < 0.01). The baseline height discrepancy was more severe in classical (−13.6 ± 7.6 cm) compared with nonclassical (−10.3 ± 3.8 cm) patients (P = 0.05). The final height discrepancy was also more severe in classical (−4.0 ± 4.6 cm) than in nonclassical (−0.3 ± 3.1 cm) patients (P < 0.01). However, the mean gain in height was not statistically different between classical (9.6 ± 6.5 cm) and nonclassical (10.0 ± 3.4 cm) patients.

### Adrenal hormone control

During the GH treatment period, there were 12 subjects with good adrenal control, 19 subjects with fair adrenal control, and three subjects with poor adrenal control. The mean gain in height was lower in subjects with poor adrenal control (4.0 ± 3.0 cm) than in subjects with good adrenal control (10.7 ± 3.8 cm, P < 0.01) and in subjects with fair adrenal control (10.1 ± 6.3 cm, P < 0.05).

### Dose of hydrocortisone

There was no change in the dose of hydrocortisone with GH treatment. At the start of GH treatment, the mean dose of hydrocortisone was 12.0 ± 4.4 mg/m² · d. At the midpoint of GH treatment, the mean dose was 12.0 mg ± 4.4 mg/m² · d. At the end of GH treatment, the mean dose was 11.9 ± 4.8 mg/m² · d.

### Comparison with historical patients

In our database of historical CAH patients who never received GH or LHRHα, 208 patients (71 males, 137 females) have reached final adult height. Of those 208 patients, 115 (55.3%) reached a minimum final adult height within 1 SD of their mid-parental target height (36.6% of males and 65% of females reached their target range). In contrast, among the 34 GH-treated CAH patients, 29 (85.3%) reached a final adult height within 1 SD of mid-parental target height (73.7% of treated males and 100% of treated females reached their target range) (Table 5).

### Compliance and adverse events

Twenty-nine of the study participants remained in the study until completion. Five subjects discontinued GH be-

### Table 3. Final adult height (males compared with females)

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 19)</th>
<th>Female (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good:fair:poor (control)</td>
<td>3:13:3</td>
<td>9:6:0</td>
<td></td>
</tr>
<tr>
<td>Complete:partial treatmenta</td>
<td>15:4</td>
<td>14:1</td>
<td></td>
</tr>
<tr>
<td>GH treatment duration (yr)</td>
<td>5.6 (1.8)</td>
<td>4.5 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>−0.5 (0.7)</td>
<td>−0.07 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Gain in height (cm)</td>
<td>9.2 (6.7)</td>
<td>10.5 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Final height discrepancy (cm)</td>
<td>−4.3 (4.6)</td>
<td>−0.6 (3.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD). NS, Not significant; SV, simple-virilizing CAH; SW, salt-wasting CAH.

### Table 4. GH-treated subjects with and without LHRHα

<table>
<thead>
<tr>
<th></th>
<th>LHRHα (n = 27)</th>
<th>No LHRHα (n = 7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>16:11</td>
<td>3:4</td>
<td></td>
</tr>
<tr>
<td>Good:fair:poor (control)</td>
<td>10:14:3</td>
<td>2:5:0</td>
<td></td>
</tr>
<tr>
<td>SW:SV:NC-CAH</td>
<td>11:7:9</td>
<td>3:1:3</td>
<td></td>
</tr>
<tr>
<td>Bone age at start of GH yr</td>
<td>11.8 (1.6)</td>
<td>9.9 (2.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age at start of GH (yr)</td>
<td>8.9 (2.2)</td>
<td>7.4 (2.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gain in height (cm)</td>
<td>9.2 (5.8)</td>
<td>11.8 (4.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>−0.37 (0.8)</td>
<td>−0.07 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>GH treatment duration (yr)</td>
<td>5.1 (1.9)</td>
<td>5.2 (1.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD). NS, Not significant; SV, simple-virilizing CAH; SW, salt-wasting CAH.

### Table 5. Percentage of treated subjects who reached target height (comparison with historical CAH patients)

<table>
<thead>
<tr>
<th></th>
<th>Subjects who reached target height (n (%))a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with GH ± LHRHα (n = 34)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>29 (85.3)</td>
</tr>
<tr>
<td>Males (n = 19)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Females (n = 15)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Not treated with GH or LHRHα (n = 208)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>115 (55.3)</td>
</tr>
<tr>
<td>Males (n = 71)</td>
<td>26 (36.6)</td>
</tr>
<tr>
<td>Females (n = 137)</td>
<td>89 (65)</td>
</tr>
</tbody>
</table>

a Patients who reached a minimum final adult height of 1 SD below mid-parental target height.
fore reaching final adult height. Compliance with the study medications was monitored by interviews with parents and subjects at each visit and was additionally monitored via returned empty vials in those subjects receiving GH from Eli Lilly & Co. Reported compliance with GH therapy was more than 90% in all subjects. Reported compliance with glucocorticoid therapy remained the same.

No subjects had sustained levels of IGF-I or IGF-binding protein 3 exceeding the upper range of normal for bone age. Thyroid function and hemoglobin A1c remained normal in all subjects. One subject, after attempting a crab walk exercise (walking on all four limbs, facing upward), developed sharp lower back pain followed by subsequent paresthesia and weakness in the lower limbs. He was diagnosed with central canal stenosis at L4–L5 with central disc protrusion and cauda equina syndrome. After surgical decompression, his symptoms resolved. The cause of stenosis is unknown but was likely congenital. During the recovery period, the same subject developed bilateral carpal tunnel syndrome, which subsided when GH was discontinued for 1 wk and then resumed at a lower dose. There were no reports of other adverse events, e.g. diabetes mellitus, malignancy, slipped capital femoral epiphyses, or pseudotumor cerebri.

Discussion

This report is particularly significant because it is a comprehensive expansion of the only study that addresses the long-term use of GH in the CAH population. With significantly more subjects, it has given us more statistical power and has allowed us to analyze more variables that may affect stature in patients with CAH.

Replacement glucocorticoid therapy remains the customary treatment for patients with CAH. The growth-suppressing effects of glucocorticoids, however, combined with early epiphyseal fusion from the high androgens in CAH, limit the height potential of patients affected with CAH. Although quite often tall as children, many patients with CAH complete growth prematurely and are ultimately short as adults. We have previously reported an improvement in predicted height in CAH patients treated with GH as well as an improvement in final adult height in those treated with a combination of GH and LHRHa (16, 40). This report is the first to demonstrate a significant improvement in final adult height outcome in CAH children who are treated with GH alone or in combination with LHRHa.

The goal of combined treatment with GH and LHRHa is to target the various problems causing short stature in children with CAH. GH counters the deceleration in growth velocity that often accompanies glucocorticoid therapy, whereas LHRHa suppresses central puberty to prevent premature epiphyseal closure. In this report, not all subjects were treated with LHRHa, and those who did receive combination therapy did not have a greater gain in height. However, the subjects treated with LHRHa started GH therapy at a later age than those treated with GH alone. As shown by the significant negative correlation between gain in height and age at the start of GH, subjects who started GH at a younger age had a greater improvement in height. Perhaps those subjects who started GH early enough were able to gain enough in height that they did not require LHRHa. Because it does not appear that LHRHa added any clear benefit to GH therapy, the decision to treat with LHRHa should be based on the age of the patient and the social impact of precocious puberty rather than adding LHRHa for the sole purpose of increasing the gain in height.

Severity of disease (classical vs. nonclassical) did not appear to be a factor in the response to treatment. Nonclassical CAH (NC-CAH) is a milder form of CAH with clinical and hormonal criteria that distinguish it from classical CAH, and it can present at any age. In contrast to classical CAH, females with NC-CAH are born with normal genitalia. Symptoms vary widely in NC-CAH; some patients may present with premature pubarche, whereas others may not present until adolescence or adulthood with hirsutism, irregular menses, acne, or infertility (43, 44). Many patients with nonclassical CAH are asymptomatic and do not require any treatment (45). In this study, however, only patients who fulfilled the inclusion criteria were included; therefore, the nonclassical patients who were included in the study were on the more severe end of the spectrum. The compromised height predictions and advanced bone ages in these particular subjects may also stem from the fact that nonclassical patients generally are not identified in the neonatal period and do not have the benefit of being treated with glucocorticoid replacement from birth, as do classical patients. This delay in treatment may explain why some nonclassical patients appear to have a similar risk as classical patients for advanced bone age and compromised height prediction. In terms of effectiveness of GH treatment, the gain in height was similar for both groups.

Adrenal control during the GH treatment period played an important role on the gain in height. Patients with poor adrenal control did not have as much gain in height from the GH therapy than those who were in fair or good adrenal control. Although the increased adrenal androgens in those with poor adrenal control could have had a synergistic effect with the GH on growth velocity, the effect of high androgens on bone age advancement appeared to
have a more negative impact on ultimate height. It seems that as long as adrenal control was fair, GH treatment was equally effective in improving height outcome. It is also possible that the patients found to have poor adrenal control were noncompliant with both their glucocorticoid replacement and their GH treatment, even though the reported compliance with GH was over 90%.

Despite the notable improvement in final height outcome, the mean final height of the males was still 4 cm below mid-parental target height, whereas the females reached a mean final adult height only 0.6 cm below mid-parental target height. Both males and females achieved similar gains in height with GH treatment, but because the males started off with a greater height discrepancy than the females (−13.5 cm vs. −11.1 cm), their final height discrepancy was also greater. There were proportionately more classical patients within the males than the females. The males were also not in as good adrenal control as the females. Among the males, there were three subjects with poor adrenal control, whereas among the females, none had poor control. Because subjects with poor adrenal control had a significantly lower gain in height, those subjects may account, at least in part, for the discrepancy between the males and females. There were also four males who discontinued GH early, and only one female subject who discontinued early. Another possibility is that, in general, males with CAH do not fare as well as females with CAH in terms of height outcome. A possible explanation is that before newborn screening, males with simple-virilizing CAH were diagnosed at a later age than females with classical CAH (who were picked up due to ambiguous genitalia) and did not have the benefit of hydrocortisone treatment from infancy. Most males with salt-wasting CAH would have presented with salt wasting in the first few weeks of life, but others may have died in infancy before they could be diagnosed. Another consideration is the accuracy of predicted heights in patients with CAH. In a review of 49 CAH patients comparing final adult height with predicted height at the start of puberty, final adult height in boys correlated with Bayley-Pinneau average (which is typically lower than Bayley-Pinneau accelerated), whereas in girls it correlated with Bayley-Pinneau accelerated (25). It is possible that glucocorticoid treatment in CAH patients increases fat mass, thereby increasing aromatization of androgens to estrogens; the effect of aromatized estrogens from adrenal androgens may have a more detrimental effect on growth and final adult height in boys (who are not normally exposed to so much estrogen) than in girls (in whom the adrenal contribution to estrogen production is relatively minor compared with the ovarian production of estrogen during puberty).

In our previous publications in 2001 and 2005, we compared treated subjects to historical controls (who did not receive GH or LHRHa), who were matched for age, bone age, type of CAH, gender, and target height. The group of historical controls was matched to the treated group for gender, severity of CAH, bone age, target height, and height discrepancy. Although some subjects did end up with a final adult height higher than initial predicted height, most reached a final adult height that was even lower than predicted height. As a group, the mean final adult height was 0.5 cm below initial predicted height. In this updated report of 34 treated subjects who have reached final adult height, however, there are not enough data on historical patients to match for all of these variables. Therefore, subjects were compared with their own pretreatment predictions. Because predicted height (particularly using the Bayley-Pinneau accelerated method) in CAH patients, if anything, tends to be overly optimistic, we believe that a substantial increase in adult height compared with the initial predicted height is truly significant.

The findings presented in this study indicate that GH alone or in combination with LHRHα is an effective therapy for improving final adult height in CAH. The promising results from this study pave the way for other potential treatment strategies, because there are still a variety of factors that play a role in growth and stature in patients with CAH that have not been completely elucidated. The greater height discrepancy in males compared with females with CAH opens up the possibility of exploring other therapeutic options, such as the use of aromatase inhibitors in males with CAH.

A limitation of this study is that it was not a randomized controlled study. In this initial pilot study, we chose not to randomize subjects because as the first study of its kind, our goal was to determine possible efficacy. Another limitation of this study is the relatively small sample size. In the 2010 Endocrine Society CAH Clinical Practice Guideline, GH treatment was not recommended as standard treatment for CAH patients due to limited data on the subject (45). However, guidelines are constantly being revised and modified as new data are presented. Further larger studies in a randomized controlled design are needed before definitive conclusions can be drawn. The authors stress that not all CAH patients require intervention to improve their final adult height. This report describes only subjects with significantly compromised predicted heights due to advanced bone ages. With newborn screening now in place in all 50 states in the United States, early diagnosis and treatment as well as compliance with optimal replacement therapy and close monitoring, particularly during puberty, would ideally preempt the need for intervention; however, for those subjects who, despite early
treatment (or for nonclassical patients who present late), are slated for an adult height well below the population mean, GH may be a viable option for them. The optimal treatment for improving stature in patients with CAH continues to be an important area of clinical investigation.

Acknowledgments

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This work was supported in part by U.S. Public Health Service Grant HD-00072, General Clinical Research Center Grant 06020, and Eli Lilly, Co.

Disclosure Summary: The authors have nothing to disclose.

References


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