Growth Hormone Treatment and Its Effect on Height in Pediatric Patients with Different Genotypes of Prader-Willi Syndrome

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Purpose: Differences in phenotypes between the two most common subtypes of Prader-Willi syndrome (PWS) indicate that a distinct response to growth hormone (GH) treatment may exist. To test this hypothesis, we compared the results of GH treatment in individuals with PWS due to uniparental disomy (UPD) to those of individuals with deletions.

Methods: Sixty-five children with PWS who had been treated with GH for more than two years were included in this study. Twenty-one individuals were confirmed as having UPD and 44 individuals had a deletion. Height, body weight, body mass index (BMI), and insulin like growth factor-1 (IGF-I) measurements were recorded before GH treatment and at intervals of 12 months thereafter.

Results: After two years of GH therapy, no significant differences were noted for yearly improvements in height standard deviation scores (SDS) between the groups (second year SDS, 0.93 ± 0.94; deletion, 0.84 ± 1.31; UPD, \( P = 0.717 \)). Body weight SDS, BMI SDS, and IGF-I SDS also showed no differences between the two groups.

Conclusion: Our study showed no significant differences in yearly improvements in height SDS between the deletion and UPD groups, at least for the first two years.

Key Words: Prader-Willi syndrome; Growth hormone; Sequence deletion; Uniparental disomy

Introduction

Prader-Willi syndrome (PWS) is a complex multisystemic genetic disorder characterized by hypothalamic-pituitary dysfunction. Its key features include hypotonia, short stature, hyperphagia, hypogonadism, scoliosis, and psychological and behavioral problems. PWS can result from several factors, including the absence of expression of the paternal regions of chromosome 15q11-q13, maternal uniparental disomy (UPD), an imprinting center mutation, or translocations involving chromosome 15\(^1\).\(^2\)

Comparisons between deletion and UPD patients have indicated that hypopigmentation is more often seen in deletion patients, while increased maternal age and lower birth length are more frequent in UPD subjects\(^3\). Oto et al.\(^4\) reported that growth hormone secretion was lower in children with UPD than in those with deletions.

In order to determine whether differential responses to growth hormone (GH) treatment occur in patients with PWS caused by deletion or UPD, we compared the height, body weight, body mass index (BMI), and insulin like growth factor-I (IGF-I) level of patients after two years of GH treatment.
Materials and Methods

1. Patients

The study included 67 Korean PWS patients (40 boys and 27 girls, 4 months to 13 years of age) who were treated with growth hormone at the endocrinology department of Samsung Medical Center between May 2004 and May 2012. The children were treated with recombinant human GH, at a mean dosage of 1.0 mg/m²/day, administered in daily subcutaneous injection for more than 2 years.

Diagnosis of all PWS patients was confirmed by methylation-specific PCR (polymerase chain reaction), then we performed fluorescence in situ hybridization in order to detect the interstitial deletion of the 15q11-13 region. In addition, microsatellite analysis was undertaken in order to confirm the UPD in non-deletion group. Among these patients, 44 had deletions and 21 had UPD type PWS. Two patients had imprinting defects and were excluded from this study.

2. Clinical, anthropometric and laboratory data of the patients

The clinical and anthropometric data of the patients were compared by retrospective examination of their medical records. A wall-mounted stadiometer was used to measure height. Supine length was measured in infants younger than three years of age. Height was measured in triplicate and the mean value was recorded. Growth was analyzed by calculating the height standard deviation scores (SDS), body weight SDS, and body mass index (BMI) SDS using the Korean Pediatric Growth Chart 2007 reference standards. Height, body weight, and BMI measurements were recorded before GH treatment and at intervals of 12 months thereafter.

Serum insulin-like growth factor-I (IGF-I) levels were monitored at the initiation, after 12 months, and after 24 months of GH treatment. The IGF-I values were converted to values corresponding to the reference SDS values for Korean children.

3. Statistical analysis

Statistical analyses were performed using SPSS for Window (version 15.0.1, SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as the means and standard deviations, unless specified otherwise, and P-values < 0.05 were considered significant. Data were analyzed by comparing patients with the deletion type of PWS to patients with the UPD type. Differences between genotype groups were assessed using the median regression analysis with Bonferroni correction.

Results

1. Characteristics of PWS patients with deletion and UPD

Among 65 PWS patients, 40 were boys and 25 were girls. In the deletion group, 29 were boys and 15 were girls. In the UPD group, 11 were boys and 10 were girls. The height SDS, body weight SDS, BMI SDS, and IGF-I SDS at the initiation of GH treatment were similar between the deletion and UPD groups. No significant differences were noted in age of diagnosis or age at the start of GH treatment (Table 1).

2. Anthropometric data and IGF-1 level in the deletion and UPD

In both deletion and UPD group, height SDS increased significantly after two years of GH treatment. Yearly improvements in height SDS were not significantly different between the two groups. No significant differences were found for body weight SDS, BMI SDS, IGF-I SDS changes (Table 2).

Discussion

Our study found no genotype-dependent differences in the

Table 1. Characteristics of PWS patients with deletions and UPD

<table>
<thead>
<tr>
<th></th>
<th>Deletion</th>
<th>UPD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>44 (29:15)</td>
<td>21 (11:10)</td>
<td></td>
</tr>
<tr>
<td>Age of diagnosis (yr)</td>
<td>4.2 ± 3.74</td>
<td>3.67 ± 3.63</td>
<td>P = 0.587</td>
</tr>
<tr>
<td>Age at start of GH (yr)</td>
<td>5.3 ± 3.57</td>
<td>4.18 ± 3.65</td>
<td>P = 0.243</td>
</tr>
<tr>
<td>Ht SDS baseline</td>
<td>-1.39 ± 1.7</td>
<td>-1.17 ± 1.29</td>
<td>P = 0.537</td>
</tr>
<tr>
<td>Bwt SDS baseline</td>
<td>-0.27 ± 2.3</td>
<td>0.14 ± 0.22</td>
<td>P = 0.454</td>
</tr>
<tr>
<td>BMI SDS baseline</td>
<td>1.17 ± 2.74</td>
<td>1.65 ± 2.84</td>
<td>P = 0.481</td>
</tr>
<tr>
<td>IGF-1 SDS baseline</td>
<td>-0.81 ± 1.81</td>
<td>-0.68 ± 1.44</td>
<td>P = 0.442</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SDS.

Abbreviations: UPD, uniparental disomy; GH, growth hormone; Ht-SDS, height standard deviation score; Bwt-SDS, body weight standard deviation score; BMI-SDS, body mass index standard deviation score; IGF-1, insulin-like growth factor-1.

Table 2. Anthropometric data and IGF-1 level in the deletion and UPD group

<table>
<thead>
<tr>
<th></th>
<th>Deletion</th>
<th>UPD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht ∆SDS after 1 yr</td>
<td>0.51 ± 2.1</td>
<td>0.58 ± 0.95</td>
<td>P = 0.517</td>
</tr>
<tr>
<td>Ht ∆SDS after 2 yr</td>
<td>0.12 ± 1.3</td>
<td>0.09 ± 1.23</td>
<td>P = 0.717</td>
</tr>
<tr>
<td>Bwt ∆SDS after 1 yr</td>
<td>0.45 ± 1.58</td>
<td>0.44 ± 1.27</td>
<td>P = 0.385</td>
</tr>
<tr>
<td>Bwt ∆SDS after 2 yr</td>
<td>0.21 ± 2.45</td>
<td>0.17 ± 1.96</td>
<td>P = 0.75</td>
</tr>
<tr>
<td>BMI ∆SDS after 1 yr</td>
<td>0.42 ± 1.28</td>
<td>0.01 ± 1.99</td>
<td>P = 0.479</td>
</tr>
<tr>
<td>BMI ∆SDS after 2 yr</td>
<td>0.11 ± 0.97</td>
<td>0.01 ± 2.1</td>
<td>P = 0.245</td>
</tr>
<tr>
<td>IGF-1 ∆SDS after 1 yr</td>
<td>1.75 ± 1.85</td>
<td>2.34 ± 2.46</td>
<td>P = 0.659</td>
</tr>
<tr>
<td>IGF-1 ∆SDS after 2 yr</td>
<td>1.98 ± 1.8</td>
<td>2.39 ± 2.79</td>
<td>P = 0.274</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SDS.

Abbreviations: UPD, uniparental disomy; Ht-SDS, height standard deviation score; Bwt-SDS, body weight standard deviation score; BMI-SDS, body mass index standard deviation score; IGF-1, insulin-like growth factor-1.
response to the GH treatment between patients with deletion and UPD type PWS, even though distinct phenotypic differences existed between these two groups in a previously published study.\textsuperscript{6}

However, Grugni et al.\textsuperscript{7} reported that GH secretion was lower in adult patients with UPD than in patients with deletions. Oto et al.\textsuperscript{6} also found differences in GH secretion between subtypes in children with PWS\textsuperscript{6}, but they were unable to conclude that GH was more efficacious in the UPD group.

The phenotypic differences observed between patients with deletion and UPD of PWS may be related to the underlying differences in gene expression of the genetic subtypes.\textsuperscript{9,10} In the deletion type of PWS patients, all of the non-imprinted genes located within the deleted region are present only as a single copy\textsuperscript{9,10}. Haploid insufficiency could therefore be a possible mechanism contributing to the PWS phenotype in patients with a deletion. Maternal disomy, on the other hand, would not result in haploid insufficiency; rather, it would result in a double dose of any imprinted genes that are normally silenced in the paternally inherited homolog of chromosome 15, but that remain active in the maternal homolog\textsuperscript{9,11,12}.

Consideration of the main types of abnormality found in PWS suggests that a difference in clinical phenotype should be found, due to the presence of a single vs. two copies of active genes in 15q11q13\textsuperscript{11}. A milder manifestation of the phenotype would normally be expected in disomy, compared with deletions of an imprinted region, as the presence of excess genomic material is less harmful than a loss.\textsuperscript{3,10} Gunay-Aygun et al.\textsuperscript{10} reported that the mean age at diagnosis was significantly higher in patients with PWS due to UPD than to deletion. The average age of their deletion group at diagnosis was 3.76 years while that of the disomy group was 9.29 years. However, we did not observe a similar trend in our study, as the mean age at diagnosis was 4.2 ± 3.74 for deletion and 3.67 ± 3.63 for UPD.

Oto et al.\textsuperscript{6} expected a genotype-dependent difference in the response to GH treatment because responses to an insulin stimulation test were significantly lower in the UPD group than in the deletion group. However, they found that the peak GH level following insulin stimulation was at the low-normal range in the deletion group (peak GH levels, 11.1 ± 8.6 ng/mL: deletion, 3.6 ± 2.2 ng/mL: UPD, P = 0.0013) and they could not demonstrate a similar between-subgroup difference by an arginine provocation test (peak GH levels, 9.4 ± 6.8 ng/mL: deletion, 6.32 ± 4.6 ng/mL: UPD, P = 0.092)\textsuperscript{6}.

We evaluated the effect of GH on height gain in Korean children with different genotypes of PWS. Our study also showed no significant difference in yearly improvements in height SDS between the deletion and UPD groups, at least for the first two years. The reason is not clear why similar yearly growth rates were seen in patients with PWS due to a deletion and due to UPD, even though genotype-dependent differences were clearly evident.

Polymorphism in the GH receptors might play a role in the heterogeneous responses to GH treatment. Park et al.\textsuperscript{15} reported that patients with PWS and an exon-3 deletion polymorphism in the GH receptor gene had significantly greater height SDSs and higher IGF-1 level before GH treatment. We have previously analyzed the distribution of GHR (growth hormone receptor) alleles in the patients with PWS and their height SDS after 2 years of GH treatment (data not shown). We found no significant difference in the distribution of GHR alleles between PWS patients with deletion and PWS patients with UPD (deletion type: fl/fl 29 patients, fl/d3 15 patients vs. UPD type: fl/fl 15 patients, fl/d3 6 patients). We also found no statistically significant differences with regard to the different GHR genotypes.

Considering all of the data on children with PWS published to date, we conclude that GH secretion alone does not explain the individual variability in responsiveness to GH. The differential results must be due to other genetic factors or to environmental factors such as nourishment and nutritional status.

References