**Effects of Growth Hormone Treatment on Height, Weight, and Obesity in Taiwanese Patients with Prader-Willi Syndrome**

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**Introduction**

Prader-Willi syndrome (PWS) is a congenital disorder characterized by short stature, childhood-onset obesity, hyperphagia, neonatal hypotonia, hypogonadism, developmental delay, typical facial appearance, and behavioral problems. Most patients have hypothalamic-pituitary dysfunction and growth hormone (GH) deficiency. The genetic basis of PWS is loss of paternal gene expression in the PWS-critical region on 15q11-13. Approximately 70–75% of cases result from deletion of this region in the paternal chromosome 15, 25–28% from maternal uniparental disomy (UPD), and 2–5% from a mutation or deletion in the imprinting center or other imprinting defect. The most common dysmorphic features of PWS are short stature and obesity.

**Background:** Information regarding the efficacy of growth hormone (GH) therapy in Asian Prader-Willi syndrome (PWS) patients is lacking. We report our experience with GH treatment in children with PWS in Taiwan.

**Methods:** Forty-six PWS patients (27 males, 19 females; age range, 1 year 4 months to 13 years 7 months) who received and/or who are currently receiving GH treatment (0.1 IU/kg/day subcutaneously) for a period from 1 year to 3 years were retrospectively analyzed. We evaluated height, weight, body mass index (BMI) and Rohrer index, before and after GH treatment.

**Results:** After patients had received GH for 1, 2 and 3 years, a significant improvement in mean height standard deviation score (SDS) was noted from $-1.24$ to $-0.31$ ($p<0.01$), $0.00$ ($p<0.001$) and $-0.26$ ($p<0.001$), respectively. Mean BMI SDS decreased significantly from $1.93$ to $1.13$ ($p<0.05$) after 1 year of treatment; however, no significant changes were observed afterward. Mean Rohrer index decreased significantly, from $224.2$ to $186.6$ ($p<0.001$), $178.9$ ($p<0.001$) and $169.3$ ($p<0.001$). No significant gender or genotype pattern differences were noted among the 4 parameters examined.

**Conclusion:** This 3-year, retrospective study indicates that PWS patients benefit from GH therapy in height increase and improved body composition. [J Chin Med Assoc 2008;71(6):305–309]

**Key Words:** growth hormone, height, obesity, Prader-Willi syndrome, Rohrer index
Data from short-term\textsuperscript{10–17} and longer-term studies\textsuperscript{18–21} in Western countries have shown that GH therapy improves growth rate and body composition. However, information regarding the long-term efficacy of GH treatment for Asian PWS patients is limited.\textsuperscript{22} Thus, the aim of this study was to evaluate whether GH treatment could improve growth rate, standard deviation score (SDS) of height, weight and body mass index (BMI), and Rohrer index.

### Methods

#### Subject selection

Forty-six patients with PWS (27 males, 19 females; age range, 1 year 4 months to 13 years 7 months) who received and/or who are currently receiving GH treatment (0.1 IU/kg/day subcutaneously) from August 2002 through June 2007 in 8 medical centers in Taiwan were enrolled in this study. These medical institutions were Mackay Memorial Hospital, Taipei Tzu Chi Hospital, Kaohsiung Medical University Hospital, China Medical University Hospital, Kaohsiung Veterans General Hospital, Cathay General Hospital, Chang-Gung Children’s Hospital and Taipei City Hospital. GH treatment was started at between 2 months and 10 years 10 months of age. The duration of GH therapy ranged from 1 year to 4 years and 11 months. For each patient, an informed written consent was signed by at least 1 parent. Each patient received a complete genetic analysis. The study was approved by the ethics committee of Mackay Memorial Hospital, Taipei, Taiwan.

#### Data and statistical analyses

We compared height, weight, BMI (weight in kg divided by height in meters squared) and Rohrer index (weight in kg divided by height in meters cubed $\times$ 10) before and after GH treatment. SDS was derived by subtracting the population mean from an individual raw score and then dividing the difference by the population standard deviation. Height, weight and BMI were also calculated as SDS according to the standard growth tables for Taiwanese children.\textsuperscript{23–25} Two-tailed paired $t$ statistics were used to test for statistical significance. The effects of gender and genotype pattern on changes in height SDS, weight SDS, BMI SDS and Rohrer index after GH treatment were analyzed using 2-way analysis of variance (ANOVA), with gender (males vs. females) and genotype pattern (deletion vs. UPD) as main effects. Differences were considered to be statistically significant when $p<0.05$.

### Results

The clinical profiles of the 46 participants are summarized in Table 1. The mean age at the start of GH treatment was 4.3 $\pm$ 3.0 years. With regard to the underlying genetic defect, deletion was found in 35 (76%) patients, maternal UPD in 9 (20%), and an imprinting center deletion or an imprinting defect in 2 (4%).

#### Changes in growth rate for children beyond 3 years of age

The growth velocity of children reaches its highest value during the first 2–3 years of life before puberty, and slows to about 6 cm/year during middle childhood.\textsuperscript{26} In order to minimize the statistical bias, we selected children beyond 3 years of age and before puberty (30 cases) to depict the curve of height velocity before and during GH treatment (Figure 1). After patients had received GH treatment for 1, 2 and 3 years, their height velocities improved from 4.00 $\pm$ 1.92 to 10.36 $\pm$ 2.37 cm/year ($p<0.001$), 7.47 $\pm$ 1.68 cm/year ($p<0.001$), and 6.38 $\pm$ 1.31 cm/year ($p<0.05$), respectively.

#### Changes in height SDS, weight SDS, BMI SDS and Rohrer index

After patients had received GH treatment for 1, 2 and 3 years, height SDS improved from $-1.24 \pm 1.44$ to $-0.31 \pm 1.25$ ($p<0.01$), 0.00 $\pm$ 1.11 ($p<0.001$), and $-0.26 \pm 0.43$ ($p<0.001$), respectively (Figure 2A). Weight SDS changed non-significantly from 1.11 $\pm$ 2.36 to 1.26 $\pm$ 2.41 ($p>0.05$) and to 0.98 $\pm$ 1.12 ($p>0.05$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline ($n=46$)</th>
<th>1 year ($n=46$)</th>
<th>$p$</th>
<th>2 years ($n=39$)</th>
<th>$p$</th>
<th>3 years ($n=17$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH SDS</td>
<td>$-1.24 \pm 1.44$</td>
<td>$-0.31 \pm 1.25$</td>
<td>$&lt;0.01$</td>
<td>$0.00 \pm 1.11$</td>
<td>$&lt;0.001$</td>
<td>$-0.26 \pm 0.43$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>BW SDS</td>
<td>$1.11 \pm 2.36$</td>
<td>$1.26 \pm 2.41$</td>
<td>NS</td>
<td>$1.47 \pm 2.15$</td>
<td>NS</td>
<td>$0.98 \pm 1.12$</td>
<td>NS</td>
</tr>
<tr>
<td>BMI SD</td>
<td>$1.93 \pm 2.24$</td>
<td>$1.13 \pm 2.29$</td>
<td>$&lt;0.05$</td>
<td>$1.44 \pm 2.06$</td>
<td>NS</td>
<td>$1.09 \pm 1.27$</td>
<td>NS</td>
</tr>
<tr>
<td>Rohrer index (kg/m$^3$)</td>
<td>$224.2 \pm 35.2$</td>
<td>$186.6 \pm 35.6$</td>
<td>$&lt;0.001$</td>
<td>$178.9 \pm 63.3$</td>
<td>$&lt;0.001$</td>
<td>$169.3 \pm 86.7$</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
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BH = body height; SDS = standard deviation score; BW = body weight; BMI = body mass index; NS = not significant.
after 1 year and 3 years of GH treatment, respectively (Figure 2B). In contrast, BMI SDS showed a significant decrease from 1.93 ± 2.24 to 1.13 ± 2.29 (p < 0.05) after 1 year of treatment, but exhibited no significant differences afterwards (Figure 2C). The Rohrer index decreased significantly from 224.2 ± 35.2 to 186.6 ± 35.6 (p < 0.001) at year 1, and to 178.9 ± 63.3 (p < 0.001) at year 2, and to 169.3 ± 86.7 (p < 0.001) at year 3 of treatment (Figure 2D).

**Analysis of response to GH treatment**

No significant gender or genotype pattern effect was found for any of the growth parameters analyzed.

**Adverse events**

One child died while receiving GH treatment. She had been treated with GH for more than 23 months. She died at the age of 6 years and 1 month due to pneumonia with respiratory failure. In our study, no child developed diabetes mellitus or scoliosis while receiving GH treatment.

**Discussion**

This study was a retrospective analysis of 46 cases of PWS collected over a 5-year period (2002–2007) in 8 medical centers in Taiwan. Earlier studies in Western countries had demonstrated the clinical benefits of GH therapy in children with PWS, including improvement of linear growth, body composition, fat utilization, physical strength and agility. The response to GH therapy of children with PWS was greatest during the first 12 months in relation to increased linear growth rate, decreased body fat, and increased lean body mass. However, between months 12 and 36, the growth rate slowed down; these results were consistent with those of previous longer-term studies. This reduction in response to GH therapy has also been documented in other disorders treated with prolonged GH therapy, such as Turner syndrome, intrauterine growth restriction, chronic renal failure, and idiopathic short stature.

In our study, the improvement of height SDS was still statistically significant after 3 years of GH therapy, which indicated that the efficacy of GH lasted for at least 3 years. Our data demonstrate that although GH therapy did not give rise to statistically significant changes in weight SDS, there was a significant decrease in BMI SDS in the first year of treatment. These findings are in agreement with those reported by Obata et al, Davies et al, and Lindgren and Ritzen.

Although Mei et al reported that for children and adolescents aged 2–19 years, the performance of BMI-for-age was better than that of Rohrer index-for-age in predicting overweight, some evidence still showed that the Rohrer index was independent of age, and represents a better parameter than BMI in predicting body fatness from childhood through adolescence. In comparison with BMI, which generally increases with age from childhood through adolescence, it indicates that improvement in Rohrer index showed an actual improvement of obesity. Generally, Rohrer index is one of the parameters to predict body fatness in children. Our study indicates that GH therapy led to a significant decrease in Rohrer index, suggesting that GH treatment probably improved the degree of obesity in patients with PWS. This finding is in accordance with that of Obata et al.

The study of Obata et al showed that PWS males might gain more height than PWS females with GH therapy. They compared the mean final height of male and female patients with GH therapy to those without GH therapy, finding 10.3 cm and 6.5 cm gains, respectively, after GH treatment. However, in our 1-year data, we did not find significant difference in height SDS change between male and female patients. More longer-term studies are required to clarify this point. To the best of our knowledge, our study provides the first evidence that no significant genotype pattern difference was noted among the 4 parameters examined.

Sudden unexpected deaths were reported in patients with PWS who received GH therapy, and the causes
remained diverse, including bronchopneumonia, respiratory insufficiency and sleep apnea. Our patient died at the age of 6 years and 1 month due to pneumonia with respiratory failure after receiving GH therapy for more than 23 months. Scoliosis and diabetes mellitus were the most commonly reported adverse effects, but we did not find such events at the time of this study.

PWS is not an indication for GH treatment in many countries, so long-term data on final height and safety are at present limited. The limitations of our data were that it was a retrospective and uncontrolled study, however, it is the first report of GH therapy in Taiwanese patients with PWS. Since May 2004, GH therapy has been endorsed by the National Health Insurance for the treatment of PWS in Taiwan.

More long-term efficacy and safety data will be needed to determine whether GH treatment in children with PWS actually improves their quality of life.

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**References**


