Prader-Willi syndrome: a single center’s experience in Korea

Yea Ji Kim, MD1, Chong Kun Cheon, MD, PhD1,2,3

1Department of Pediatrics, Pusan National University School of Medicine, Yangsan, 2Department of Pediatrics, Pediatric Endocrinology and Metabolism, Pusan National University Children’s Hospital, Yangsan, 3Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea

Purpose: Prader-Willi syndrome (PWS) is a complex genetic disorder that results from the lack of paternally expressed genes in the chromosome 15q11–q13 region. This study was performed to delineate the clinical features of PWS infants and toddlers and the effects of two-year growth hormone (GH) treatment according to gender and age at the start of treatment.

Methods: The clinical characteristics and the results of the GH treatment were reviewed retrospectively for 30 PWS patients diagnosed by molecular genetic testing and clinical manifestations.

Results: The mean age at diagnosis with PWS was 13.7 months (2–47 months of age). All patients showed the characteristics of facial dysmorphism, including brown hair and almond-shaped eyes. Most patients showed developmental delays/mental retardation (93.3%), cryptorchidism (75%), feeding problems in infancy (73.3%), and neonatal or infantile hypotonia (66.7%). Among 30 patients, 14 PWS infants and toddlers had been treated with GH for more than two years. Two years of GH treatment resulted in an improvement in head circumference-standard deviation score (HC-SDS), body weight-SDS, insulin-like growth factor-1 (IGF-1) SDS, IGF binding protein-3 (IGFBP-3) SDS, lean body mass, and bone mineral content, especially in IGFBP-3 SDS and motor development in PWS patients younger than two years of age. There was significant increase in IGF-1 SDS and IGFBP-3 SDS among male PWS patients after GH treatment.

Conclusion: Our study showed increases in IGFBP-3 SDS and an improvement in motor development among individuals under two years of age after GH treatment, and significant difference in IGF-1 SDS and IGFBP-3 SDS by gender.

Key words: Prader-Willi syndrome, Growth hormone, Clinical manifestations

Introduction

Prader-Willi syndrome (PWS) is a complex genetic disorder that results from the lack of paternally expressed genes in the chromosome 15q11–q13 region caused by a deletion of the paternal copy (70%), maternal uniparental disomy (UPD) (25%), an imprinting center defect, or balanced translocation1-3. The estimated prevalence of PWS is difficult to ascertain, but several studies suggest that it is one in 10,000–30,000 live births4,5. PWS is characterized by atypical facial features, hypotonia, feeding problems, developmental delays, hypogonadism, short stature, obesity, and behavioral and learning disturbances3,6.

PWS patients are troubled with growth hormone (GH) insufficiency6. Therefore, GH treatment is used to improve body composition and growth during childhood. Reports have demonstrated that GH treatment in older PWS children has resulted not only in a remarkable growth response but also in a dramatic improvement in body composition,
with a decline in fat percentage and an increment in lean body mass (LBM), resulting in increased muscle strength and agility.\textsuperscript{3,7,8} Several studies on psychomotor development in PWS infants have demonstrated the improvement in body composition, motor development, and cognitive development during GH treatment.\textsuperscript{4,8} Although there have been several reports on the clinical characteristics and the effects of GH treatment on PWS patients,\textsuperscript{9,10} few reports have compared GH treatment effects according to gender and age at the start of GH treatment in Korean PWS patients. Therefore, the primary object of this study was to delineate the clinical manifestations of Korean PWS infants and toddlers and examine the effects of GH treatment according to gender and age at the start of GH treatment at a single center.

Materials and methods

1. Patients

We retrospectively analyzed the medical records of 30 patients with PWS (16 boys, 14 girls) who were diagnosed using molecular genetic testing, including methylation specific polymerase chain reaction and fluorescence in situ hybridization, as well as their clinical features at the Endocrinology Department of Pusan National University Children’s Hospital between March 2009 and August 2013. In addition, microsatellite analysis was performed to confirm the UPD in nondeletion individuals. Among 30 patients with PWS, 22 patients were treated with recombinant human GH (Genotropin, Pfizer, New York, NY, USA). Among individuals under two years of age, GH treatment was started at a low dose, such as 0.25–0.30 mg/m\textsuperscript{2}/day or 0.009–0.012 mg/kg/day and increased during the first weeks and months to reach the standard replacement GH dose of approximately 1.0 mg/m\textsuperscript{2}/day or 0.035 mg/kg/day, administered in daily subcutaneous injections, and only 14 patients (eight boys, six girls) received GH treatment for more than two years.

2. Methods

The patients visited the outpatient clinic for follow-up every three months and their height, weight, complete blood cell counts, routine chemistry, and thyroid function were checked. Height was measured using a Harpenden stadiometer marked to the nearest 0.1 cm and weight was recorded to the nearest 0.1 kg with an electric scale. Supine length was measured in infants younger than three years of age. Growth was analyzed by calculating the height standard deviation scores (SDS), body weight SDS, and body mass index (BMI) SDS according to the 2007 growth reference of Korean children and adolescents by the Korean Pediatric Society and Korea Centers for Disease Control and Prevention. Dual x-ray absorptiometry was used to calculate the body component ratio including LBM, fat percentage, bone mineral content (BMC), and bone mineral density (BMD). Height, body weight, head circumference, and BMI measurements were recorded before GH treatment and at intervals of 12 months thereafter. Psychomotor development was evaluated using the Denver developmental screening test (DDST) in GH treated patients with PWS by age at the start of GH treatment. Test results of psychomotor development were expressed as developmental age divided by chronological age and multiplied by 100, reflecting the percentage of the expected development (%ed) for that age. Changes in motor and mental development are expressed as percentage of change over 24 months (development at 24 months minus development at start, divided by development at start, multiplied by 100). Written consent was obtained from all participants who provided identifiable samples.

3. Statistical analysis

The Wilcoxon signed rank test was used to compare data before and after GH treatment. Mann-Whitney analysis was used to assess the effects of GH treatment according to gender and age in 14 patients with PWS. Differences were considered statistically significant when \( P < 0.05 \). All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

Results

1. Clinical characteristics in PWS patients

Thirty patients were diagnosed with PWS during a period of four years and six months. The sex ratio had a similar proportion of females and males: sixteen patients (53.3%) were male and fourteen (46.7%) were female. The mean age at presentation was 2.3 months (0–4.2 months of age). The mean age at the diagnosis was 13.7 months (2–47 months of age). The mean follow-up period was 3.5 years (2.3–4.4 years). Twenty eight patients (93.3%) had a paternal deletion, and the other two (6.7%) had a UPD. Phenotypic characterization of all patients was performed and is summarized in Table 1. All patients showed the characteristics of facial dysmorphism, including blond or brown hair, almond-shaped eyes, and a thin upper lip. Most patients showed developmental delays/mental retardation (93.3%), cryptorchidism (75%), feeding problems in infancy (73.3%), and neonatal or infantile hypotonia (66.7%).

Ophtalmologic problems were common, particularly strabismus (33.3%). The following brain abnormalities were present in three patients (10.0%): cortical dysplasia (3.3%), an absence of neurohypophysis (3.3%), and periventricular
leukomalacia (3.3%). Skeletal abnormalities, including scoliosis (26.7%) and flexible flat foot (6.7%), were also observed. Obesity and seizures were also observed in five patients (16.7%) and four patients (13.3%), respectively.

Table 1. Clinical features of patients with Prader-Willi syndrome (n=30)

| Variable                              | Value                        |
|---------------------------------------|------------------------------|
| Age at presentation (mo)              | 2.3±1.9                      |
| Age at diagnosis (mo)                 | 13.7±30.2                    |
| Sex                                   |                              |
| Male                                  | 16 (53.3)                    |
| Female                                | 14 (46.7)                    |
| Gestational age (wk)                  | 39.2±2.8                     |
| Birth weight (g)                      | 2.7±0.5                      |
| Delivery                              |                              |
| Vaginal delivery                      | 14 (46.7)                    |
| Cesarean section                      | 16 (53.3)                    |
| Age of parents (yr)                   |                              |
| Mother                                | 30.7±3.2                     |
| Father                                | 33.5±4.1                     |
| Genetic cause                         |                              |
| Deletion                              | 28 (93.3)                    |
| Uniparental disomy                    | 2 (6.7)                      |
| Symptoms                              |                              |
| Feeding problems in infancy           | 22 (73.3)                    |
| Developmental delays or mental retardation | 28 (93.3)                  |
| Neonatal/infantile hypotonia          | 20 (66.7)                    |
| Sleep disturbance/apnea               | 4 (13.3)                     |
| Seizure                               | 4 (13.3)                     |
| Vigorous appetite                     | 4 (13.3)                     |
| Obesity                               | 5 (16.7)                     |
| Characteristic facies                 |                              |
| Blonde hair/ brown hair               | 30 (100)                     |
| Almond-shaped eyes                    | 30 (100)                     |
| Strabismus                            | 10 (33.3)                    |
| Small hands/feet                      | 8 (26.7)                     |
| Scoliosis                             | 8 (26.7)                     |
| Gait disturbance, wide base          | 4 (13.3)                     |
| Flexible flat foot (pes planus)       | 2 (6.7)                      |
| Cryptorchidism                        | 12 (75)                      |
| Brain abnormalities                   | 3 (10.0)                     |
| Cortical dysplasia                    | 1 (3.3)                      |
| Absence of neurohypophysis            | 1 (3.3)                      |
| Periventricular leukomalacia          | 1 (3.3)                      |
| Patients with GH treatment            | 22 (73.3)                    |

Values are presented as mean±standard deviation or number (%). GH, growth hormone.

Table 2. Anthropometric characteristics, body composition, and laboratory data of patients with Prader-Willi syndrome before and after growth hormone treatment (n=14)

| Variable                              | Baseline | After 2 yr | P value |
|---------------------------------------|----------|------------|---------|
| Ht-SDS                                 | –1.20±1.34 | –0.72±1.01 | 0.056   |
| Bwt-SDS                                | –0.82±1.60 | –0.07±1.17 | 0.048   |
| BMI-SDS                                | 0.66±1.92  | 0.47±1.22  | 0.779   |
| HC-SDS                                 | –1.81±1.30 | –0.77±0.83 | 0.004   |
| LBM (g)                                | 10,156.55±6,330.24 | 12,272.52±4,379.82 | 0.001  |
| Body fat (%)                           | 34.72±8.00 | 32.42±7.86 | 0.701   |
| BMC (g)                                | 484.51±222.06 | 656.16±229.60 | 0.001  |
| BMD (Z score)                          | 0.39±1.22  | 1.00±1.12  | 0.067   |
| HbA1c (%)                              | 5.42±0.17  | 5.52±0.24  | 0.192   |
| Glucose (mg/dL)                        | 92.79±14.89 | 96.25±37.51 | 0.071   |
| Insulin (IU/mL)                        | 11.01±8.33 | 16.34±11.99 | 0.177   |
| TG (mg/dL)                             | 122.33±35.61 | 92.71±37.51 | 0.074   |
| T-cholesterol (mg/dL)                  | 179.50±31.64 | 180.78±18.32 | 0.875  |
| Free T4 (ng/dL)                        | 1.11±0.20  | 1.14±0.15  | 0.834   |
| TSH (mIU/mL)                           | 3.24±2.13  | 2.64±1.15  | 0.510   |
| IGF-1 SDS                              | –0.08±0.65 | 0.77±0.81  | 0.002   |
| IGFBP-3 SDS                            | –0.18±0.24 | 0.36±0.51  | 0.052   |

Values are presented as mean±standard deviation score. Ht-SDS, height standard deviation score; Bwt, body weight; BMI, body mass index; HC, head circumference; LBM, lean body mass; BMC, bone mineral content; BMD, bone mineral density; HbA1c, hemoglobin A1c; TG, triglyceride; T-cholesterol, total cholesterol; Free T4, free thyroxine; TSH, thyroid-stimulating hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3.

2. Anthropometric data and IGF-1/IGFBP3 levels in GH-treated PWS subjects

The mean age at the start of GH treatment in the 14 PWS patients was 2.6 years (6.4–73.5 months). The mean treatment duration was 3.5 years (2.4–4.5 years). After two years of GH treatment, height –SDS (Ht-SDS) increased from –1.20±1.34 to –0.72±1.01 (P=0.056). Head circumference–SDS (HC-SDS) also increased from –1.81±1.30 to –0.77±0.83 (P=0.004). Body weight–SDS (Bwt-SDS) increased from –0.82±1.60 to –0.07±1.17 (P=0.048). LBM (g) increased from 10,156.55±6,330.24 to 12,272.52±4,379.82 (P=0.001). BMC (g) increased from 484.51±222.06 to 656.16±229.60 (P=0.001). BMD (z score) seems to increase from 0.39±1.22 to 1.00±1.12 (P=0.067). The body fat percentage tended to decrease from 34.72±8.00 to 32.42±7.86, but it was not statistically significant. IGF-1 SDS and IGF binding protein-3 (IGFBP-3) SDS increased from –0.08±0.65 to 0.77±0.81 and –0.18±0.24 to 0.36±0.51 (P=0.002) (Table 2).

3. Comparison of GH treatment by age at the start of GH treatment

We compared the results of GH treatment for children under two years (n=6) (10.66±5.76 months) and older than two years of age (n=8) (43.65±30.2 months) at the start of treatment. There were significant increases in IGFBP-3 SDS among individuals...
under two years of age compared with individuals older than two years of age after GH treatment ($P=0.014$) (Table 3). Psychomotor data were obtained using the DDST in GH-treated patients with PWS according to the age of GH start (Table 4). The changes in both gross and fine motor development were observed during the second year of study among individuals younger than two years of age who obtained GH therapy: Change was from 62.37%±13.68% to 77.02%±14.97% ($P=0.028$) in gross motor development and from 63.00%±10.96% to 77.11%±11.63% ($P=0.028$) in fine motor development, respectively (Figs. 1, 2).

4. Comparison of GH treatment of PWS patients by gender

The efficacies of GH treatment for male and female patients with PWS were compared (Table 5), and there was significant difference in insulin-like growth factor-1 (IGF-1) SDS and IGFBP-3 SDS among male PWS patients.

5. Complications associated with GH treatment

GH was well tolerated and did not affect sleep-related breathing disorders, glucose control, and insulin and thyroid hormone levels. Among 14 patients receiving GH treatment, only one showed scoliosis resulting in the cessation of GH treatment.

### Table 3. Comparison of outcome variables by age at the start of growth hormone treatment (n=14)

| Variable                  | <2 yr (n=6) | After 2 yr | ≥2 yr (n=8) | After 2 yr | P value |
|---------------------------|-------------|------------|-------------|------------|---------|
| Mean age (mo)             | 10.66±5.76  | 43.65±19.34| 13.075±6.907| 14.037±5.011| 0.063   |
| Ht-SDS                    | –0.21±1.12  | –1.95±1.00 | –1.02±1.14  | 0.366      |
| Bwt-SDS                   | –0.84±1.41  | –0.80±1.82 | –0.09±1.30  | 0.606      |
| BMI-SDS                   | NA          | 0.66±1.92  | 0.85±1.15   | 0.796      |
| HC-SDS                    | –1.88±1.72  | –1.73±0.70 | –1.02±1.14  | 0.366      |
| LBM (g)                   | 6,265±2,364 | 10,214±2,543| 13,075±6.907| 14.037±5.011| 0.063   |
| Body fat (%)              | 35.33±8.59  | 34.26±8.10 | 33.84±7.43  | 0.253      |
| BMC (g)                   | 331.71±134.61| 524.36±165.14| 769.09±224.62| 0.568      |
| BMD (z score)             | 1.8±0.21    | 0.21±1.18  | 0.78±1.14   | 0.269      |
| HbA1c (%)                 | 5.43±0.19   | 5.41±1.73  | 5.59±0.16   | 0.242      |
| Glucose (mg/dL)           | 92.83±6.15  | 92.75±19.60| 95.00±17.00 | 0.846      |
| Insulin (IU/mL)           | 7.10±2.83   | 13.94±10.01| 17.03±10.92 | 0.897      |
| TG (mg/dL)                | 115.20±18.59| 127.43±44.97| 90.2±38.79 | 0.948      |
| T-cholesterol (mg/dL)     | 177.50±45.07| 181.00±20.05| 178.63±13.91| 0.796      |
| FreeT4 (ng/dL)            | 0.99±0.22   | 1.20±0.13  | 1.20±0.15   | 1.000      |
| TSH (ulU/mL)              | 3.30±2.36   | 3.20±2.11  | 2.82±1.24   | 0.606      |
| IGF-1 SDS                 | 0.02±0.67   | 0.15±0.66  | 0.35±0.66   | 0.302      |
| IGFBP-3 SDS               | –0.20±0.20  | –0.17±0.28 | 0.02±0.18   | 0.014      |

Values are presented as mean±standard deviation score.

Ht-SDS, height standard deviation score; Bwt, body weight; BMI, body mass index; HC, head circumference; LBM, lean body mass; BMC, bone mineral content; BMD, bone mineral density; HbA1c, hemoglobin A1c; TG, triglyceride; T-cholesterol, total cholesterol; FreeT4, free thyroxine; TSH, thyroid-stimulating hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein; NA, not applicable.

### Table 4. Baseline and 24-month data on psychomotor development in patients with Prader-Willi syndrome treated with growth hormone by age at the start of treatment

| Variable                  | GH treated patients with PWS | GH treated patients with PWS |
|---------------------------|------------------------------|------------------------------|
|                           | <2 yr (n=6)                  | ≥2 yr (n=8)                  |
|                           | Baseline                     | After 2 yr                   | Baseline                     | After 2 yr |
| Gross motor development (%ed) | 62.37±13.68                  | 77.02±14.97                  | 70.52±11.14                  | 74.91±11.43 |
| Fine motor development (%ed)  | 63.00±10.96                  | 77.11±11.63                  | 71.45±7.56                   | 76.03±10.12 |
| Language development (%ed)    | 65.30±11.69                  | 77.92±12.74                  | 66.20±10.38                  | 69.69±8.65  |
| Personal-social development (%ed) | 69.31±17.84                  | 76.69±8.69                   | 73.35±10.38                  | 76.56±12.34 |

Values are presented as mean±standard deviation score.

GH, growth hormone; PWS, Prader-Willi syndrome; %ed, the percentage of the expected development for that age.
Discussion

This study was performed to delineate the phenotypic characterization of Korean PWS infants and toddlers and assess their response to two years of GH treatment according to gender and age at the start of treatment, which would allow a comprehensive understanding of the natural course of PWS and the effects of GH treatment. PWS is characterized by a number of signs and symptoms. In the present study, most patients showed developmental delays or mental retardation, cryptorchidism, feeding problems in infancy, and neonatal or infantile hypotonia. Of interest, strabismus, scoliosis, and obesity were infrequent (33.3%, 26.7%, and 16.7%, respectively).

Perhaps this is because most of the patients enrolled in this study were infants and toddlers. In addition, seizures developed in four patients (13.3%) with PWS within one year of age and well controlled by antiepileptic drugs in all patients.

GH treatment in PWS has resulted in improved body composition (increase in LBM, lack of increase in fat mass) and cognitive function in those who have been treated. In this study, increase of HC-SDS, Bwt-SDS, BMC, LBM, IGF-1 SDS, and IGFBP-3 SDS after two years of GH treatment in PWS infants and toddlers was observed. In particular, a meaningful increase in IGFBP-3 SDS was shown in PWS patients under two years of age when compared to those over two years of age after GH treatment. In addition, BMI-SDS seems to decrease more in PWS female patients than in PWS male patients after GH treatment.

Brain growth during infancy and early childhood seems to be more important than fetal brain growth in determining cognitive function. After two years of GH therapy, we found a significant increase of HC–SDS in PWS patients. This suggests that cognitive function may improve in PWS patients treated with GH. However, a correlation between the changes in mental development and HC was not assessed. In the present study, PWS patients who received GH treatment when they were under two years of age seemed to have improved the language and personal-social development compared to those who received GH treatment when they were older than two years of age, although there was no significant correlation statistically.

Obata et al. showed that PWS males with GH treatment may have greater height increases than PWS females do with the treatment. Lin et al. compared the mean final height of male and female patients with GH treatment to those without GH treatment, finding 10.3- and 6.5-cm gains, respectively, after GH treatment. Although there was significant increase in IGF-1 SDS and IGFBP-3 SDS among male PWS patients comparing with female PWS patients in this study, further long-term follow-up research on the mean final height of male and female patients with and without GH treatment is required.

Reus et al. hypothesized that GH treatment could improve the effect of specialized physical training on motor development in patients with PWS. Motor problems in PWS patients are presumed to be related to an abnormal high fat muscle ratio. This ratio is important for overcoming gravitational forces and performing the stepping reflex. In PWS patients, however, from birth onwards, fat mass increases and muscle mass decreases. In the present study, 6 patients under two years of age with PWS who received GH treatment have improved motor development compared to those older than two years of age who received GH treatment. Even if GH treatment has a preserving effect on LBM and BMC, it still has no proven effect on “functional” muscle strength. Reus et al. also reported that noninvasive muscle ultrasound scans and functional magnetic resonance images
should be conducted to gain more insight into the relationship between GH treatment and muscle strength. Therefore, additional research on muscle strength measurements using noninvasive methods before and after GH treatment in Korean PWS patients is needed. In addition, although LBM and BMC have increased in the present study, decreases in body fat percentage and BMI-SDS were not shown in spite of two years of GH treatment. Therefore, it is necessary to control body weight and fat mass with lifestyle changes, diet, and exercise rather than GH treatment.

GH treatment is more often being initiated earlier than in the past. Reported results indicate that GH treatment in PWS has been advantageous when given at the age of 4 to 6 months of age,8,19). However, no consensus has been reached on the ideal age of treatment initiation, although researchers have agreed on the benefits of treating before the onset of obesity, which often begins by two years of age5). Considering the increase in IGFBP-3 SDS and an improvement in motor development in PWS patients under two years of age after GH treatment in the present study, it might be beneficial to begin GH treatment as soon as possible.

Although we performed a comprehensive review of the clinical findings of PWS, our study has several limitations. First, the number of patients enrolled in the present study was too small and the period was too short to represent the general clinical spectrum and the effects of GH treatment on Korean PWS patients. Second, a prospective study is required to confirm these benefits due to the limitations of a retrospective study.

A previous study that was conducted in Korea reported increment of Ht-SDS, Bwt-SDS, and decrement of body fat percentage after two years of GH treatment in PWS patients older than two years of age11). Meanwhile, our study was the first to examine the effects of GH treatment according to gender and age at the start of GH treatment, as well as the clinical spectrum in Korean PWS infants and toddlers.

In conclusion, our study showed increases in IGFBP-3 SDS and an improvement in motor development among individuals under two years of age after GH treatment, and difference in IGF-1 SDS and IGFBP-3 SDS by gender. Much longer-term evaluations of a large number of patients are necessary to further investigate the effects of GH treatment in PWS infants and toddlers.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

**Acknowledgments**
We thank the patients and their families for participating in this study, which was supported by a 2-Year Research Grant of Pusan National University.

References

1. Butler MG, Brandau DT, Theodoro M, Garg U. Cortisol levels in Prader-Willi syndrome support changes in routine care. Am J Med Genet A 2009;149A:138-9.
2. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M; speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 2008;93:4183-97.
3. de Lind van Wijngaarden RF, Siemensma EP, Festen DA, Otten BJ, van Mil EG, et al. Efficacy and safety of long-term continuous growth hormone treatment in children with Prader-Willi syndrome. J Clin Endocrinol Metab 2009;94:4205-15.
4. Reus L, Pelzer BJ, Otten BJ, Siemensma EP, van Alfen-van der Velden JA, Festen DA, et al. Growth hormone combined with child-specific motor training improves motor development in infants with Prader-Willi syndrome: a randomized controlled trial. Res Dev Disabil 2013;34:3092-103.
5. Deal CL, Tony M, Hoybye C, Allen DB, Tauber M, Christiansen JS; et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab 2013;98:E1072-87.
6. Cassidy SB, Driscoll DJ. Prader-Willi syndrome. Eur J Hum Genet. 2009;17:3-13.
7. Festen DA, de Lind van Wijngaarden R, van Eekelen M, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome. Clin Endocrinol (Oxf) 2008;69:443-51.
8. Festen DA, Wevers M, Lindgren AC, Bohm B, Otten BJ, Wit JM, et al. Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader-Willi syndrome. Clin Endocrinol (Oxf) 2008;68:919-25.
9. Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. Am J Med Genet A 2007;143:443-8.
10. Jin DK. Endocrine problems in children with Prader-Willi syndrome: special review on associated genetic aspects and early growth hormone treatment. Korean J Pediatr 2012;55:224-31.
11. Kim SJ, Cho JB, Kwak MJ, Kwon EK, Paik KH, Jin DK. Effects and adverse-effects of growth hormone therapy in children with Prader-Willi syndrome: a two year study. Korean J Pediatr 2008;51:742-6.
12. Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Troeman ZC, van Alfen-van der Velden AA, Otten BJ, Rotteveel J, et al. Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: a randomized controlled trial and longitudinal study. J Clin Endocrinol Metab 2012;97:2307-14.
13. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. J Clin Endocrinol Metab 2002;87:1581-5.
14. Ohata K, Sakazume S, Yoshino A, Murakami N, Sakuta R. Effects of 5 years growth hormone treatment in patients with Prader-Willi syndrome. J Pediatr Endocrinol Metab 2003;16:155-62.
15. Lin HY, Lin SP, Tsai LP, Chao MC, Chen MR, Chuang CK, et al. Effects of growth hormone treatment on height, weight, and obesity in Taiwanese patients with Prader-Willi syndrome. J Chin Med Assoc 2008;71:305-9.
16. Vestergaard P, Kristensen K, Bruun JM, Ostergaard JR, Heickendorff L, Mosekilde L, et al. Reduced bone mineral density and increased bone turnover in Prader-Willi syndrome compared with controls matched for sex and body mass index: a cross-sectional study. J Pediatr 2004;144:614-9.
17. Hedstrom M, Saaf M, Brosjo E, Hurtig C, Sjoberg K, Wesslau A, et al. Positive effects of short-term growth hormone treatment on lean body mass and BMC after a hip fracture: a double-blind placebo-controlled pilot study in 20 patients. Acta Orthop Scand 2004;75:394-401.
18. Reus L, Zwarts M, van Vlimmeren LA, Willemsen MA, Otten BJ, Nijhuis-van der Sanden MW. Motor problems in Prader-Willi syndrome: a systematic review on body composition and neuromuscular functioning. Neurosci Biobehav Rev 2011;35:956-69.
19. Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB. Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome. J Clin Endocrinol Metab 2010;95:1131-6.