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Growth Outcome and Metabolic Profile of PWS Patients Treated with GH and Differences between AGA and SGA Group

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Background: Prader-Willi syndrome (PWS) is a complex genetic disease associated with growth impairment, severe obesity and metabolic dysfunctions. High proportion of PWS patients are born small for gestational age (SGA) than normal children, which also increase the risk of growth impairment and metabolic dysfunction in PWS. We aimed to compare growth outcome and metabolic profiles between SGA and appropriate for gestational age (AGA) PWS patients. **Methods:** Data of 55 PWS children and adults aged more than 2 years old (32 male and 23 female, age 2-18.8 years) from single center were studied. Only patients who were treated with GH were included. The clinical characteristics and laboratory findings were reviewed retrospectively. **Results:** Among 55 subjects, 39 had 15q11-13 deletion and 16 had uniparental disomy (UPD). Twenty (36.3%) were born SGA. All patients received GH treatment, and 11 (20%) discontinued GH treatment. Mean age at GH treatment initiation was 2.5 (range 0.3-12.4) years, and mean duration of treatment was 6.3 (range 1.0-11.3) years. Current height-SDS (-0.36 vs -0.16) and BMI-SDS (1.44 vs 1.33) did not differ between AGA and SGA group. Two patients in SGA group, but none in AGA group had diabetes mellitus. Mean glucose level was also higher in SGA group (100.1 vs 114.4 mg/dL). **Conclusion:** Our report gives an overview of growth profile and metabolic dysfunctions recorded in GH treated PWS patients. Growth profile did not differ between AGA and SGA group. Glucose level was higher in SGA group, so more careful monitoring and prevention for DM will be required in SGA group.

Key words: Prader-Willi syndrome, Growth outcome, SGA

ORIGINAL ARTICLE

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INTRODUCTION

Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by severe obesity and neurodevelopmental abnormality. PWS results from absence of expression of imprinted genes in the chromosome 15q11-q13 region, caused by deletion of the paternal copy (70%), maternal uniparental disomy (UPD) (25%), an imprinting center defect (1-3%), or balanced translocation [1-3].

It is known that about 90% of patients with PWS have short stature [4]. When growth hormone is not replaced, average adult height in male and female patients with PWS is 155 cm and 148 cm, respectively [5,6]. But when treated with growth hormone (GH) through childhood, children with PWS are able to achieve normal adult height [5,7]. So, recombinant human growth hormone (rhGH) was FDA approved in the United States in 2000 for treatment of short stature and growth failure due to PWS [8].

PWS patients are frequently born small for gestational age (SGA), and body mass index (BMI) of PWS are approximately 15–20% lower than those of their normal mates [9]. SGA is also a risk factor of short adult height. Among SGA children, 8-12% will have a short stature at 2 years of life, and these children have a higher risk of short stature in adulthood [10,11]. So, GH treatment is indicated for children born SGA, who have persistent short stature (less than or equal to –2

Table 1. Clinical characteristics

Variable	All patients (n=55)	SGA (n=20)	AGA (n=35)	*P* value
Male (n, %)	32 (58.2)	15 (75.0)	17 (48.6)	0.056
Current age (yr)	9.0±4.0	8.8±3.8	9.2±4.1	0.749
Age at GH initiation (yr)	2.2±2.6	1.6±1.8	2.5±2.9	0.157
Duration of GH treatment (yr)	6.3±3.0	7.0±2.6	5.9±3.0	0.176
Gestational age (wk)	38.6±1.9	38.8±1.3	38.5±2.2	0.445
Birth weight (kg)	2.68±0.46	2.38±0.29	2.85±0.45	<0.001
Genetic causes				0.466
deletion (n, %)	39 (70.9)	13 (65.0)	26 (74.3)	
uniparental disomy (n, %)	16 (29.1)	7 (35.0)	9 (25.7)	

SGA, small for gestational age; AGA, adequate for gestational age; GH, growth hormone.

SDS according to sex and age for general population for sex and population) at the age of 3–4 years [12].

In this study, we compared growth and metabolic profile and effect of GH between SGA and AGA PWS.

METHODS

Subjects and method

We obtained data of PWS children who visited our hospital from 2007-2020. Inclusion criteria were genetically confirmed PWS patients aged more than 2 years who used GH more than 6 months.

As our routine clinical practice for PWS patients, height (Ht), weight, body mass index (BMI), glucose, HbA1c, and lipid level were checked at regular follow-up with 3-6 months interval. By retrospective chart review, we obtained anthropometric parameters and laboratory findings at the time of GH initiation and at last follow up. All standard deviation scores (SDS) of anthropometric measurements were calculated using a Korean growth standard [13]. SGA was defined by birthweight below the 10th percentile for babies of the same gestational age and sex. Adequate for gestational age (AGA) was defined by birthweight 10-90th percentile for babies of the same gestational age and sex. Obesity was defined by BMI more than 95th percentile for the children of the same age and sex. Diabetes mellitus (DM) was defined as fasting blood glucose ≥126 mg/dL or random glucose ≥200 mg/dL or taking DM medication. Dyslipidemia was defined as total cholesterol ≥200 mg/dL or triglyceride ≥150 mg/dL or LDL cholesterol ≥130 mg/dL, or taking lipid lowering medication.

Statistical analysis

All data are presented as n(%) for the mean±standard deviation. Differences in anthropometric measurements and treatment response between groups were compared using Student t test and Wilcoxon rank sum test. All statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA), and *P* values <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Total fifty-five patients were enrolled in this study. Twenty were born SGA and thirty-five were born AGA. Thirty-two (58.2%) were male, and age was. 9.0±4.0 years. Patients used growth hormone for 6.3±3.0 years. Genetic causes were deletion in thirty-nine (70.9%) and uniparental disomy in 16 (29.1%) patients. There were no differences in clinical characteristics between SGA and AGA group (Table 1).

Anthropometric characteristics and current laboratory data

In all subjects, Ht-SDS at GH initiation and current Ht-SDS were -0.91±1.60 and -0.29±1.34, respectively. BMI-SDS at GH initiation and current BMI-SDS were 1.64±1.97 and 1.33±2.42, respectively. HbA1c and total cholesterol were 5.4±0.3% and 184.0±29.3 mg/dL, respectively. SGA children had higher glucose level than AGA children (114.4±27.8 vs. 100.1±16.0 mg/dL. *P*=0.019). There were no differences in other anthropometric and laboratory parameters between SGA and AGA group (Table 2).

GH treatment effect and metabolic dysfunction

We compared growth effect and metabolic profile. Current Ht-SDS and ΔHt-SDS were -029±1.34 and 0.66±1.50, respectively. ΔBMI-SDS was -0.40±1.88. There were no differences between SGA with AGA group (Table 3).

Table 2. Anthropometric characteristics and current laboratory data

Variable	All (n=55)	SGA (n=20)	AGA (n=35)	*P* value
Ht-SDS at GH initiation	-0.91±1.60	-1.23±1.26	-0.77±1.73	0.394
Current Ht-SDS	-0.29±1.34	-0.16±1.16	-0.36±1.44	0.613
BMI-SDS at GH initiation	1.64±1.97	1.33±2.42	1.78±1.85	0.693
Current BMI-SDS	1.40±1.19	1.33±1.20	1.44±1.21	0.752
HbA1c (%)	5.4±0.3	5.46±0.43	5.42±0.24	0.669
Glucose (mg/dL)	105.4±22.0	114.4±27.8	100.1±16.0	0.019
Triglyceride (mg/dL)	111.2±66.2	103.8±39.8	115.6±72.4	0.507
Total Cholesterol (mg/dL)	184.0±29.3	184.7±28.8	182.7±30.7	0.803
LDL (mg/dL)	105.9±25.2	104.6±24.3	106.6±26.0	0.783

Ht, height; SDS, standard deviation score; BMI, body mass index; LDL, low density lipoprotein.

Table 3. GH treatment effect and metabolic dysfunction

Variable	All patients (n=55)	SGA (n=20)	AGA (n=35)	*P* value
Current Ht-SDS	-029±1.34	-0.16±1.16	-0.36±1.44	0.613
ΔHt-SDS (current–GH initiation)	0.66±1.50	1.05±1.32	0.50±1.56	0.273
ΔBMI-SDS (current–GH initiation)	-0.40±1.88	-0.55±3.03	-0.33±1.27	0.884
DM (n, %)	2 (3.6)	2 (10.0)	0	0.128
Overweight/obesity (n, %)	34 (61.8)	13 (68.4)	21 (65.6)	0.838
Dyslipidemia (n, %)	21 (38.2)	7 (35.0)	14 (40.0)	0.714

Ht, height; SDS, standard deviation score; BMI, body mass index; DM, diabetes mellitus.

DISCUSSION

Our study compared GH treatment effect and metabolic profile between SGA and AGA PWS children. Our study is, as we know, the first study which compared GH treatment effect between SGA and AGA PWS children. Our study involved relatively large number of patients in single center, which can maximize homogeneity in patients or treatment.

Growth effect of GH in SGA children is thought to be lesser than in AGA children. Miazza et al. [14] compared growth effect of GH in SGA and AGA children. They reported that height velocity was higher in AGA-GHD children during the first year of treatment. Nonetheless, GH treatment in short children born SGA has shown a beneficial, growth-promoting effect in both the short-and long-term [15].

Our study has several limitations. We did not compare GH-treated with not-GH treated group, because most of PWS children in our clinic received GH therapy. And we did not compare predicted adult height or final height. These should be further explored to get effect of GH more precisely. For metabolic effect, we did not compare metabolic profile before and after GH, and compared only current metabolic profile. But in our data, SGA children had higher fasting glucose level, and only SGA patients had DM. This gives strength to our hypothesis that SGA PWS children are prone to metabolic disorder, especially impaired glucose metabolism.

In conclusion, our study describes growth response to GH and metabolic profiles, and differences among SGA and AGA PWS groups. The results of this study provide useful suggestions to make better decisions to start and optimize GH treatment in PWS children.

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CONFLICTS OF INTEREST

None.

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