ORIGINAL RESEARCH PAPER

Endocrinology

RESPONSES TO GROWTH HORMONE THERAPY IN PATIENTS WITH PRADER-WILLI SYNDROME: A SINGLE CENTER EXPERIENCE

KEY WORDS: Adenoid hypertrophy, growth hormone therapy, Prader-Willi Syndrome, scoliosis

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ABSTRACT

Prader Willi Syndrome (PWS) is a paternally expressed human imprinting disorder. PWS is one of growth hormone (GH) indications which will be beneficial in terms of metabolic and neurodevelopmental status. We presented 5 cases of PWS who had been treated with GH for minimum 1 year and establish the efficacy or safety of GH in our patients.

INTRODUCTION

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 region with three main genetic subtypes (1,2). These include paternal 15q11-q13 deletion (about 70% of cases), maternal uniparental disomy 15 or both 15s from the mother (20-30% of cases), and defects in the imprinting center (1-3%) which controls the expression of imprinted genes in this chromosome region (2). The characteristic phenotypes of PWS include severe neonatal hypotonia; early onset of hyperphagia; and development of morbid obesity, short stature, hypogonadism, learning disabilities, behavioral problems, and psychiatric phenotypes with severe consequences and difficult management issues for patients, families, and care givers (1,2). The benefits of starting growth hormone (GH) treatment as early as 2 years are well established, but there is increasing evidence of additional benefit in starting therapy between 6 and 12 months of age especially before starting obesity (1). This benefits has been reported particularly in terms of motor development, muscle, head circumference, and possibly cognition (1). The use of GH in PWS has also a positive effect on the final height and body composition (1). However, there is considerable variability in the results of GH therapy on adenoid and tonsillar hypertrophy, increased risk of sleep apnea, and even death in PWS, especially in the early stages of treatment (1). Scoliosis is seen in 30% -70% of patients, but the effect of treatment on scoliosis is also controversial (1). Reports of scoliosis worsening during GH treatment may simply reflect its natural history rather than a side effect of treatment in most cases (1). The aim of this study is to evaluate the treatment responses of patients with PWS who have started growth hormone therapy and to reveal the benefits and harms of treatment. Here, we characterize a set of clinical and biochemical results of 5 patients with PWS under GH therapy.

MATERIAL AND METHODS

Patients

Five patients (4 males, 1 female) with a confirmed diagnosis of PWS who received GH therapy and sufficient documented data were revised in this case series. A retrospective medical chart review was performed for these 5 patients. The definition of PWS required the availability of lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 region. The age of both diagnosis and GH therapy, chief complaint at admission and presenting symptoms, and other comorbidities were evaluated. Physical examination findings, pubertal status and secondary sex characteristics, presence of gonadal failure were investigated. The following clinical and laboratory parameters, including height, weight, body mass index (BMI), testicular volumes, fasting blood glucose (BG), fasting insulin, homeostatic model assessment–insulin resistance (HOMA–IR), serum lipids, total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid hormones, insulin-like growth factor I (IGF-1), insulin-like growth factor-binding protein 3 (IGFBP-3), cortisol levels were recorded. The standard deviation score (SDS) of height, weight, and body mass index (BMI) were calculated according to the reported data of Neyzi for Turkish (4). The diagnosis of a neurocognitive disorder and the need for special education were retrieved from the medical records.

GH Therapy Protocol

GH was started to all patients at a low dose of 0.009-0.012 mg/kg/day as recommended (1,3). The recommended maximum dose of 0.035 mg/kg/day or 1 mg/m2/day was obtained in 6-8 weeks (1,3). Routine otorhinolaryngology examination was done before and after 6-8 weeks of GH therapy, then repeated annually. On GH treatment, regular clinical assessment of height, weight, BMI, body composition, pubertal status, scoliosis, IGF-I, and side effects checked every 3–6 months. X-ray and orthopedic assessment was done before GH therapy and repeated according to the worsening of scoliosis. Papillary edema was also regularly checked.

RESULTS

Two of five patients had a significant reduction in body mass index (BMI) which is more than 1 SDS. Conversely, one of the remaining patients continued to gain weight despite treatment, while the BMI of other two patients remained nearly stable or sligtly decreased (Table 1). The remarkable finding was that GH therapy could not prevent the increase of BMI in only one patient, whereas it supported a preventive control in increasing of BMI in other 4 cases. Laboratory results of patients on admission and at last assesment under GH therapy were given in Table 2. Basal insulin levels was very high in case 1. During follow-up, insulin resistance was increased in 3 patients, but excess increase in insulin level was observed in case 4 (Table 2). Diabetes was not developed in any of our patients. Three patients received additional hypothyroidism treatment because of central hypothyroidism during their follow-up (Table 3). Case 3 whose BMI SDS decreased after GH therapy, had been operated three times for adenoid hypertrophy before his admission, but his adenoid vegetation under treatment did not show recurrence and his scoliosis remained stable. Case 5 also needed operation for adenoid hypertrophy nearly at the end of first year of GH therapy despite the good control of weight gain (Table 3). Although no increase of BMI SDS was seen, scoliosis progressed in case 1 and he needed operation. Three male patients were operated for undescended testis, unfortunately case 4 had bilateral orchiectomy before admission to our hospital (Table 3).The mean year of patient follow-up was 3.3 years in our study and no other serious side effects of treatment was observed during this period.

DISCUSSION

This study documented the clinical experience of GH therapy in PWS. This is the first study that evaluate all known children with PWS in Northern Cyprus. With this study, we tried to compare our PWS management protocol with literature and present the efficacy and safety of GH in our patients. It has been known that BMI remains on average below +2 SDS, in contrast to the natural course of increasing obesity in PWS (5). In our case series, GH was seem to be effective on BMI except for 1 case. Even in 1 patient, it was very surprising that the BMI decreased to normal range. On the other hand, positive effects on height SDS were observed in 3 cases, while height SDS of 2 cases regressed. However, it has reported that GH treatment in children with PWS significantly improves linear growth (5). All children with PWS has presented to have low serum IGF-I at baseline (6). Our retrospective reports showed that extremely low baseline IGF-1 was in 2 of 5 patients. The studies that try to demostrate the effects of GH on spinal curvature is still controversial (1,6). Some cases have scoliosis at baseline which improves or progress (6). Three of our cases had baseline scoliosis which one of them progressed and needed an operation. Mild to severe central and/or obstructive sleep apnea observe in 40% of children prior to GH initiation; 11% commenced GH on positive airway pressure, oxygen or both (6). All of our cases had adenoid hypertrophy. Two of them had operation before GH therapy while 1 had operation under GH therapy. PWS subjects show a high prevalence of altered glucose metabolism that appears more common in obese subjects (7). Compared to placebo, GH treatment results in similar glucose and insulin levels during oral glucose tolerance test and it has been reported that GH has no adverse effects on metabolic health profile (8). However, extremely increase in insulin levels was detected in one case whereas baseline insulin resistance was also observed in another case.

CONCLUSION

As a result, GH therapy in PWS may be an effective treatment option for weight control in most of the children with PWS. However, treatment-enhancing effects on scoliosis or adenoid hypertrophy are still controversial and close follow-up is required in this regard.

Table 1. Weight, height and body mass index (VKI) values in the clinical course of the cases

		GH Therapy		On admission				Last assesment			
Case no (sex)	Age of D (yr)	Age to start (yr)	Period (yr)	Age (yr)	W (kg)	H (cm)	BMI kg/m2	Age (yr)	W (kg)	H (cm)	BMI kg/m2
1 (M)	2	10	1.7	9.9	57.7(2.7 SDS, 99.6%)	133.5 (-0.6 SDS, 27.0%)	32.4 (3.0 SDS, 99.9%)	11.7	62.5 (1,8 SDS,95.9%)	140 (-1.2 SDS, 10.4%)	31.9 (2.6 SDS, 99.6%)
2 (F)	0.3	5.5	4.4	5.4	31.5(3.0 SDS, 99.9%)	106 (-1.2 SDS, 12.5%)	28.0 (3.8 SDS, >99.9%)	9.9	73 (3.7 SDS, > 99.9%)	147 (1.6 SDS, 94.2%)	33.8 (3.3 SDS, 99.9%)
3 (M)	1.5	6.5	3.0	6.2	27(1.6 SDS, 94.0%)	112.5 (-1.0 SDS, 16.1%)	*21.3 (2.6 SDS, 99.5%)	9.6	38.6 (1.2 SDS,88.3%)	139,5 (0.7 SDS, 76.7%)	*19.8 (1.1 SDS, 86.7%)
4 (M)	1	2.3	4.3	2.2	14(0.6 SDS, 71.2%)	82.5 (-1.8 SDS, 3.5%)	**20.6 (2.5 SDS, 99.3%)	6.6	75 (5.6 SDS, > 99.9%)	131.5 (2.5 SDS, 99.3%)	**43.4 (4.9 SDS, > 99.9%)
5 (M)	2.3	3.5	1	3.5	17(0.5 SDS, 68.4%)	96 (-1.1 SDS, 12.2%)	*18.5 (2 SDS, 97.7%)	4.4	15.5 (-0.9 SDS,19.8%)	96.8 (-2.0 SDS, 1.8 %)	*16.5 (0.6 SDS, 72.9%)

BMI: Body mass index, D: Diagnosis, F: Female, GH: Growth hormone, H: Height,M: Male, W: Weight, yr: year
**BMI SDS decreased > 1 SDS*
***BMI SDS increased > 1 SDS*

Table 2. Laboratory findings of cases during GH therapy

	Cases									
	1		2		3		4		5	
GH therapy status	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**
Laboratory										
BG mg/dl	105	90	88	84	83	87	101	104	55	79
Insulin IU/ml	*40.7	*43.2	12.2	*40.1	4.25	*17.9	*17	*93.3	2.6	5.6
HOMA-IR	10.5	9.6	2.65	8.3	0.87	3.8	4.2	23.9	0.4	1.0
HbA1c (%)	6	5.5	5.7	5.5	5	5.1	5.1	5.5	4.2	4.9
SGPT U/L	*53	*63	32	*36	15	11	25	*37	24	31
SGOT U/L	*36	*37	27	*34	21	20	31	25	26	29
TC mg/dl	*242	181	190	*222	*233	*231	164	177	*231	189
LDL mg/dl	*158	113	143	*151	143	*151	94	111	*151	148
HDL mg/dl	54	50	70	72	57	57	35	41	66	64
TG mg/dl	121	88	89	93	*210	185	*174	*194	72	82
TSH uIU/ml	2.4	1.8	2.3	2.4	2.3	3.8	3.3	2.3	2.1	2.3
Ft4 ng/dl	0.8	0.9	1.1	0.9	0.9	0.8	1.1	0.9	0.8	0.9
Cortisol µg/dl	9.2	10.1	7.9	10.9	16.9	11.1	8.6	10.2	30.6	10.7
IGF-1 ng/mL	123	537	46	568	199	457	287	477	15	110
IGFBP3 mg/L	3.1	6.2	2.9	7.5	3.8	6.3	4.9	7.3	0.8	1
LH mIU/ml	0.2	*2.6	PP	0.5	PP	0.02	PP	0.02	PP	PP
FSH mIU/ml	1.5	*7.2	PP	3.2	PP	0.05	PP	0.05	PP	PP
T nmol/L	1.9	4.0	-	-	PP	0.6	PP	0.6	PP	PP
E2 pg/mL	-	-	PP	29	-	-	-	-	-	-

BG: blood glucose, E2: Estradiol, FSH: Follicle-stimulating hormone, FT4: Free thyroxine, HDL: High density lipoprotein, HOMA–IR: Homeostatic model assessment–insulin resistance , IGF-1: insulin-like growth factor I, IGFBP3: Insulin-like growth factor-binding protein 3, LDL : Low density lipoprotein, LH: Luteinizing hormone, PP: was not checked because of prepubertal period, SGOT: Serum glutamic oxaloacetic transaminase,SGPT: Serum glutamic-pyruvic transaminase, T: total testosterone, TC: Total cholesterol, TG:Triglyceride, TSH: Thyrotrophin-Stimulating Hormone
**Higher values than references*

Table 3. Complications at baseline or during GH therapy

Case	Ophthalmic examination	Otorhinolaryngologic examination	Scoliosis	Undescended testes	Additional Therapy	Additional Problem
1	Normal	Adenoid hypertrophy present, no obstruction, no increase in follow-up	Progression (>300), had operation	Operation at 10 months Last puberty examination: A2, P2, Testis 4 ml / 4 ml	L-thyroxine therapy since 3 years old	No
2	Normal	3 times operated for obstructive apnea before GH, snoring continued, no apnea	160, orthopedic follow-up	-	No	Premature adrenarche At 7.5 yr
3	The optic disc is slightly indistinct but not papil edema.	Adenotonsillectomy before GH, no obstruction	No	3 times operated At the last examination, the left testicle 1 cc, right 0.5 cc	At 7 yr L-thyroxine treatment	No
4	Normal	Adenoid hypertrophy and obstructive sleep apnea present, no increase in follow-up	150, orthopedic follow-up	Bilateral orchiectomy at 1.5 yr	L-thyroxine treatment at the 5th month of GH	venous thrombosis, cellulite
5	Normal	Adenoid hypertrophy and obstructive sleep needed operation at 1st of GH	No	No	No	No

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