Brief Report

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One-year follow-up of thyroid function in 23 infants with Prader-Willi syndrome at a single center in China

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SUMMARY Endocrine disorders are common in patients with Prader-Willi syndrome (PWS). Whether hypothyroidism is present in patients with PWS, and especially infants and young children, remains unclear. The aims of this study were to evaluate thyroid function in patients with PWS, to assess the prevalence of thyroid dysfunction, and to evaluate the effect of growth hormone on thyroid function. Subjects were 23 patients with PWS ages 3 months to 3 years who were followed for up to one year. Four patients were lost to follow-up after the first visit. The remaining 19 patients were treated with recombinant human growth hormone (rhGH). PWS was diagnosed based on a genetic analysis. Free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH) levels were evaluated before and after growth hormone treatment. A total of 9 patients (9/23 = 39.1%) developed abnormal thyroid function. Five out of 23 patients (21.7%) had abnormal thyroid function before growth hormone treatment. Four patients developed thyroid dysfunction during the 3- to 9-month period of rhGH treatment. Of the 9 patients with abnormal thyroid function, 7 (5 boys, 2 girls) had central hypothyroidism, and the other 2 patients had subclinical hypothyroidism. TSH levels were higher in patients with PWS due to maternal uniparental disomy (UPD) than in patients with PWS due to a 15q11-q13 deletion. The prevalence of hypothyroidism was high in infants and young children with PWS. Thyroid function should be regularly monitored in patients with PWS at both diagnosis and follow-up.

Keywords Prader-Willi syndrome, thyroid function, growth hormone, hypothyroidism

1. Introduction

Prader-Willi syndrome (PWS) is a complex genomic imprinting disorder in which afflicted individuals experience physical and behavioral abnormalities. PWS is caused by the loss of expression of paternally transcribed genes in a highly imprinted region of chromosome 15q11-q13 (*1*). The most common molecular alteration is deletion of the paternal copy of the gene locus (70%), and the remaining cases result from maternal uniparental disomy (28%) and imprinting defects (2%) (*2*).

Abnormalities of the hypothalamo-pituitary axis are present in PWS (*3*). Magnetic resonance imaging studies have revealed hypothalamic-pituitary abnormalities, including anterior pituitary hypoplasia and an absent, small, or ectopic posterior pituitary gland, in more than 50% of patients with PWS (*4,5*). Whether hypothyroidism is present and whether it should be treated in PWS remains unclear, and this is especially true in infants and young children (*6-8*). This is an important question because hypothyroidism can contribute to delayed psychomotor development when present early in life and left untreated. Several studies have investigated thyroid function in children with PWS, and central hypothyroidism has been found in 20-30% of patients with PWS (*9,10*). However, thyroid function in patients with PWS needs to be further explored in infants and young children.

The current study retrospectively analyzed thyroid function in 23 patients with PWS between the ages of 3 months and 3 years from August 2014 to January 2019, and it investigated the effect of growth hormone on thyroid function by comparing the results before and 3 and 6 months after treatment with recombinant human growth hormone (rhGH).

2. Patients and Methods

2.1. Patients and blood samples

Potential subjects were 23 patients with PWS ages 3 months to 3 years. All of patients were regularly followed up at Xinhua Hospital in Shanghai, China. Height (or length) and weight were measured with the patient wearing light clothing without shoes. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as the weight in kg/height in meters squared. All of the patients had a normal thyroid-stimulating hormone (TSH) level at neonatal screening for congenital hypothyroidism. A group of 22 healthy children ages 1-3 years were served as the control group. This study was approved by the Ethics Committee of this hospital. Due to the retrospective nature of the study, informed consent was waived.

An automated chemiluminescent immunoassay was used to measure thyroid hormone levels. The reference values were 3.5-6.5 pmol/L for free triiodothyronine (FT3), 11.5-22.7 pmol/L for free thyroxine (FT4), and 0.55-4.78 μIU/mL for TSH. Thyroid function was classified as euthyroidism (normal FT4 level and TSH level ≤ 5 μIU/mL), hypothyroidism (low FT4 level and TSH level ≥ 10 μIU/mL), central hypothyroidism (low FT4 level and TSH level ≤ 5 μIU/mL), or subclinical hypothyroidism (normal FT4 level and TSH level > 5 μIU/mL).

2.2. Statistical analysis

Data were processed and statistically analyzed using SPSS 13.0 (SPSS, Chicago, IL, USA). Normally distributed data are reported as the mean ± SD, and skewed data are presented as medians. Between-group comparisons were performed using the Mann-Whitney *U*-test and Fisher's exact test for differences in proportions. $P < 0.05$ indicated a statistically significant difference.

3. Results and Discussion

Potential subjects were 23 patients with PWS (12 boys, 11 girls) ages 3 months to 3 years. The diagnosis of PWS was genetically confirmed in all of the patients. PWS was due to a 15q11-q13 deletion in 17 subjects (73.9%) and by uniparental disomy (UPD) in 6 subjects (26.1%). Four of the 23 patients (17.4%) were born prematurely, and seven patients (30.4%) were small for gestational age (SGA). The mean birth weight and length were 2.6 kg ± 0.43 kg (-2.02 ± 1.37 SD) and 48.71 cm ± 1.64 cm (-0.8 ± 0.99 SD), respectively. Patients with PWS had a median (IQR) age of 0.67 years (0.25-2.67 years). At diagnosis, the mean and SD of length and weight in patients with PWS were -1.42 ±1.51 SD and -0.8 ± 0.99 SD, respectively. Patients with PWS often had a low birth weight and were SGA (30.4%). This finding is consistent with the results of previous studies. Diene *et al.* studied 142 children with PWS (age 0.2-18.8 years) and found that the median birth weight was 2.65 kg (1.16-3.9), corresponding to -1.2 SD (-3.5 to +3.8). Thirty-seven out of 142 (30%) patients were born SGA (*10*). Mean maternal age was 30.3 ± 4.1 years. Mean paternal age was 32.3 ± 5 years. Most patients exhibited hypotonia, feeding difficulties, growth retardation, and microphallus. All boys had cryptorchidism, which had been surgically treated. One boy had congenital bilateral hip dislocation.

In contrast to several previous studies (*11-13*), the current findings revealed a relatively high prevalence of abnormal thyroid function in 5 out of 23 patients (21.7%) on the first test of thyroid function, with a higher frequency in males (4/5, 80%). The five patients were receiving substitutive therapy with L-thyroxine (Table 1, Patient 1 to Patient 5). A large population study found that 13.6% of patients (46/339) had abnormal thyroid function at subject recruitment, and abnormal thyroid function was also more common in males (27/46, 58.7%) (*7*). Another study reported that thyroid function was normal in newborn screening of infants with PWS (*14*). Moreover, that study found hypothyroidism in only one out of 21 older children (ages < 2 years) with PWS. However, the prevalence of hypothyroidism was higher in other studies. Diene *et al.* reported that 31 out of 127 subjects (24.4%) with PWS in France were diagnosed with hypothyroidism (*10*). In addition, a study of 18 patients with PWS conducted during the first 2 years of life reported that the prevalence of hypothyroidism (serum total thyroxine and/or FT4 levels below the 25th percentile of the reference population) was 72% (*15*). Studies of adult patients with PWS have reported that the frequency of hypothyroidism is 2.12% (1/47), which is similar to its frequency in the general population (*16*). Overall, thyroid function needs to be monitored when caring for infants and young children with PWS.

Four patients (Patient 6 to Patient 9, Table 1) had abnormal thyroid function during rhGH therapy for 3 to 9 months. In the current study, abnormal thyroid function was most often central hypothyroidism (7/9), suggesting that hypothalamic-pituitary-thyroid axis dysfunction might be a common feature in infants with PWS. This finding agrees with the results of most of the previous studies. Lorenzo *et al.* studied 339 patients with PWS (ages 0.2 to 50 years) and noted central hypothyroidism in 23 patients (*7*). Of those patients, 14 were under the age of 2 years. The highest prevalence of central hypothyroidism was reported by Vaiani *et al.*, with a rate of 72.2% (13/18) in a group of 18 infants with PWS (ages 0.16-2 years) (*15*). These findings indicate that there is a high incidence of transient or definitive hypothalamic-pituitary-thyroid axis dysfunction in patients with PWS.

Table 1. Abnormal thyroid function in patients with PWS before and after GH treatment

Patient no.	Status	Sex	Age (yrs)	FT3	FT4	TSH	Diagnosis	Mutation
1	Baseline	F	0.83	5.2	11.36	2.11	CEH	UPD
2	Baseline	M	0.94	4.32	10.21	2.47	CEH	DEL
3	Baseline	M	0.37	4.18	8.81	2.64	CEH	DEL
4	Baseline	M	1	2.88	9.91	2.13	CEH	DEL
5	Baseline	M	0.46	6.06	14.61	5.25	SH	DEL
6	3 months	M	1.08	4.08	8.56	3.17	CEH	DEL
7	3 months	M	0.56	5.68	14.34	5.29	SH	DEL
8	3 months	F	0.5	4.54	10.94	0.46	CEH	DEL
9	3 months	F	1.17	3.71	10.38	0.28	CEH	DEL

CEH, central hypothyroidism; DEL, 15q11-q13 deletion; F, female; FT3: free triiodothyronine; FT4, free thyroxine; M, male; SH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; UPD, uniparental disomy.

Table 2. Comparation of thyroid hormone levels in different groups of patients with PWS

Variables	PWS (n = 23)	CON (n = 22)	Boys (n = 12)	Girls (n = 11)	DEL (n = 17)	UPD (n = 6)	Baseline (n = 9)	3 months	Baseline (n = 4)	6 months
FT3 (pmol/L)	5.45 ± 0.95	5.88 ± 0.73	5.48 ± 1.152	5.42 ± 0.73	5.41 ± 1.08	5.58 ± 0.45	5.9 ± 0.75	5.77 ± 0.77	6.09 ± 0.47	6.15 ± 0.55
FT4 (pmol/L)	12.96 ± 1.92	15.91 ± 2.63	13.12 ± 2.32	12.8 ± 1.44	12.73 ± 2	13.63 ± 1.63	13.03 ± 1.17	13.09 ± 2.05	14.54 ± 1.87	14.24 ± 2.89
TSH (uIU/L)	2.066 ± 0.96	2.07 ± 0.9	2.56 ± 1.23	1.89 ± 0.64	2.01 ± 1.13	2.19 ± 0.29*	1.16 ± 0.39	1.45 ± 0.148	1.67 ± 0.39	1.45 ± 0.148

*$P < 0.05$ ($P = 0.0353$). Baseline, before growth hormone treatment; PWS, Prader-Willi syndrome; 3 months, 3 months of growth hormone treatment; 6 months, 6 months of growth hormone treatment.

Table 3. Comparation of the prevalence of thyroid dysfunction in different groups of patients with PWS

Variables	Boys (n = 12)	Girls (n = 11)	DEL (n = 17)	UPD (n = 6)
Prevalence of Thyroid Dysfunction	3/12 (25%)	2/11 (11.2%)	4/17 (23.5%)	1/5 (20%)
Prevalence of Normal Thyroid Function	9/12 (75%)	9/11 (81.8%)	13/17 (76.5%)	4/5 (80%)
P	0.54	0.54	0.61	0.61

Although abnormal thyroid function seemed to be more common in boys than girls, there were no differences in thyroid hormone between the two groups (Table 2), and this finding was similar to the results of previous reports (*16*). Likewise, there were no differences in the proportion of patients with thyroid dysfunction by gender or cause of PWS (Table 3). Only TSH levels were found to be higher in patients with PWS due to UPD than in patients with PWS due to a 15q11-q13 deletion. However, the mean levels of TSH were within the reference range, and there were no differences in FT3 and FT4 levels between those two groups. Thus, the clinical significance of higher TSH levels in PWS due to UPD is unclear and needs to be studied further.

All children were naive to GH treatment at the start of the study. They received a dose of 0.5 mg-1 mg rhGH/m2/day. Four patients were lost to follow-up after the first visit. After 3 months of GH treatment, 3 patients (21.4%, 3/14) developed abnormal thyroid function. Two of the three (1 boy and 1 girl) had central hypothyroidism, and the third (1 boy) had subclinical hypothyroidism. Another boy was diagnosed with central hypothyroidism after rhGH treatment for 9 months (Table 1). Daily doses of rhGH in these four patients were 0.5 mg-0.6 mg/m2/day. There were no differences in thyroid hormone levels between subjects with normal thyroid function before and 3 months and 6 months after rhGH treatment (Table 2).

A few studies have reported the effects of GH treatment on thyroid function in patients with a GH deficiency and hypopituitarism (*17-19*). GH may increase the serum FT3 level and decrease the serum FT4 level by up-regulating type 2 iodothyronine deiodinase expression (*20*). In a study of thyroid function in 75 children (ages between 6 months and 16 years) with PWS receiving rhGH therapy at a dose of 1 mg/m2/day for 1 year, 25% of the patients with PWS were found to have central hypothyroidism with significantly lower FT4 levels while TSH levels were normal (*12*). This suggests that patients with PWS were likely to suffer from hypothyroidism during GH treatment.

In conclusion, the prevalence of hypothyroidism is high in infants and young children with PWS. Thyroid

function should be regularly monitored in patients with PWS at both diagnosis and follow-up.

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