Prader-Willi Syndrome with Elevated Follicle Stimulating Hormone Levels and Diabetes Mellitus

Takashi Nagai, Naoko Mimura, Takashi Tomizawa, Tsuyoshi Monden and Masatomo Mori*

A 21-year-old man with Prader-Willi syndrome (PWS) was hospitalized due to hyperglycemia. After diet therapy and transient insulin administration, his blood glucose levels improved. Based on the fact that his urinary C-peptide levels increased, the diabetes mellitus may have been due to insulin resistance with obesity. In addition, his testes had become atrophied. Testosterone levels remained low even after human chorionic gonadotropin (HCG) administration. Luteinizing hormone (LH) levels were also low after LH releasing hormone (LHRH) administration. The LH response increased slightly after daily LHRH administration, indicating hypothalamic hypogonadism. Follicle stimulating hormone (FSH) levels were, however, high and increased after LHRH administration. The selective FSH elevation may have been due to the accompanying idiopathic oligospermia.

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Key words: testosterone, luteinizing hormone (LH), insulin resistance

Introduction

Prader-Willi syndrome (PWS) is characterized by obesity, hypotonia, hypomentia and hypogonadism. It also causes a decrease in the volume of the paraventricular nucleus-containing oxytocin neurons (1). Oxytocin neurons affect sexual behavior (2). A decrease of oxytocin neurons may also cause hyperphagia, inducing obese diabetes mellitus. Diabetes mellitus is not a diagnostic criterion for PWS but it is found in 20% of the reported cases (3). Hypogonadism in PWS is thought to be due to hypothalamic hypogonadism, since it is often associated with low gonadotropin and gonadal steroid levels (3, 4). However, variable gonadotropin response to luteinizing hormone releasing hormone (LHRH) stimulation in PWS is less frequently reported (5). We report a PWS patient who presented with diabetes mellitus and elevated FSH levels.

Case Report

A 21-year-old man had suffered for 6 weeks from thirst, polydipsia and polyuria. Hyperglycemia (402 mg/dl) was evident and he was thus admitted. He was hypotonic at birth and cried and aspirated milk weakly. Mental retardation and obesity were noted at 5 years of age. He had never had an erection nor had he ejaculated at puberty. Therefore, he had been diagnosed as PWS by a pediatrician. None of his family had had diabetes mellitus.

Physical examination showed the following findings: blood pressure 122/70, pulse rate 72/min and temperature 36.4°C. He had many dysmorphic features: central obesity (height 156 cm, weight 71 kg), small hands and feet, and a narrow bifrontal diameter and atrophied testes (17mm x 13mm x 13mm). These findings were compatible with PWS. Funduscopic examination did not show diabetic retinopathy. There was no abnormality in the neck, chest or abdomen. There was no lymphadenopathy. The grasping power was diminished (23 kg in the right and 20 kg in the left). Tendon reflexes were normal and there was no sensory abnormality. His IQ score was 77.

Urinalysis showed glycosuria (4+) without ketonuria or proteinuria. Hematology, liver function, renal function and electrolyte levels were normal. Other results were as follows: fasting blood glucose (FBG), 227 mg/dl; glycosylated hemoglobin (HbA1c), 12.3%; total cholesterol, 207 mg/dl; high density lipoprotein (HDL)-cholesterol, 42 mg/dl and triglyceride, 136 mg/dl. Urinary C-peptide (by radioimmunoassay (RIA)) levels were 98 µg/day. Anti-glutamic acid decarboxylase (GAD) antibodies (by RIP Anti-GAD Hoechst) were negative. Fluorescence in situ hybridization using SNRPN as a probe revealed no deletion in chromosome 15. The chest X-ray showed no abnormality and electrocardiogram was normal. After intrave-
nous administration of 1,000 ml physical saline with 8 units regular insulin daily for 5 days, diet therapy (1,520 kcal/day) alone normalized his blood glucose level.

Endocrinological data are shown in Table 1. Corticotropin-releasing hormone (CRH) (100 µg)-GRH (100 µg)-TRH (500 µg)-LHRH (100 µg) test showed a normal response to adrenocorticotropic hormone (ACTH), cortisol, growth hormone (GH), thyroid stimulating hormone (TSH) or prolactin. However, serum luteinizing hormone (LH) levels remained low. Basal follicle stimulating hormone (FSH) levels were high and increased after LHRH administration. The testosterone levels remained low even after human chorionic gonadotropin (HCG) (5,000u) administration.

After LHRH administration of 400 µg (morning: 200 µg, evening: 200 µg) daily for a week, LH response increased slightly, while FSH response remained almost unchanged (Fig. 1A, B). Serum levels of ACTH, GH, TSH, prolactin, LH or FSH were measured by the IRMA method, cortisol level by fluorescence polarization immunoassay, and testosterone by the RIA method.

**Discussion**

Because the patient had obesity, hypotonia, hypometria, hypogonadism and many dysmorphisms, he was diagnosed as PWS, although there was no chromosome 15 abnormality. This PWS patient had obese diabetes mellitus. The urine C-peptide increased, indicating hyperinsulinemia. Therefore his diabetes mellitus may have been due to insulin resistance with obesity in PWS (3).

Seminalysis was not available due to the lack of ejaculation. The basal testosterone levels were low and a low response after HCG administration was shown. Moreover, low basal LH levels and a low LH response after LHRH administration were detected, although the LH response increased slightly after daily LHRH administration for a week, indicating hypothalamic hypogonadism. The hypogonadism in PWS is thought to be

![Figure 1](image-url)

**Table 1. Results of CRH-GRH-TRH-LHRH Test and HCG Test**

<table>
<thead>
<tr>
<th>CRH-GRH-TRH-LHRH test</th>
<th>Time after test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone level</td>
<td>0'  15'  30'  60'  120'</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>19   58   54   29   25</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>13.1 20.2 25.3 21.7 20.4</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>1.49 9.31 9.45 6.83 4.23</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1.32 12.3 11.9 7.37 4.42</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>5.4  48.4 40.6 18.4 9.8</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>1.1  2.9  4.1  6.8  5.8</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>69.3 94.9 103.1 109.5 107.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCG test</th>
<th>Time after test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone level</td>
<td>0'  30'  60'  120'  48 hrs  72 hrs</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>163 166 174 169 179 173</td>
</tr>
</tbody>
</table>

ACTH: adrenocorticotropic hormone, GH: growth hormone, TSH: thyroid stimulating hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, HCG: human chorionic gonadotropin.
Selective FSH Elevation and Hypogonadism

primarily due to hypothalamic hypogonadism (3, 4). However, the high basal FSH levels and a hyper FSH response after LHRH administration were detected. A selective increase in FSH levels with normal LH levels after LHRH administration results from decreased gonadal production of inhibin in young men with idiopathic oligospermia (6, 7) or it occurs in the early stages of puberty (8). A few PWS patients was reported to show a selective increase of FSH levels with normal LH levels after LHRH administration (5). However, since these patients 12 years old or less and had normal testosterone levels, it is most likely that the increase of FSH levels reflected an early stage of puberty. The present 21-year-old patient is compatible with idiopathic oligospermia accompanied by PWS, a situation that has been previously unreported. A slow LHRH pulse frequency favors a selective elevation of plasma FSH, but only when plasma testosterone levels are low (9). The abnormality in LHRH pulse frequency in idiopathic oligospermia may reside not in the hypothalamic-pituitary level but rather in the testes themselves (10). Whether the patient has a slow LHRH pulse frequency is unknown. Here, after LHRH administration of 400 μg daily for a week, the LH response increased slightly. The FSH response remained almost unchanged. Releasable FSH stores may be readily depleted and not rapidly replenished compared to LH (11) by LHRH administration of 400 μg daily for one week in this patient. Hypogonadism accompanied by PWS may necessitate further investigation.

References

8) Lee PA, Migeon CJ. Puberty in boys: correlation of plasma levels of gonadotropins (LH, FSH), androgens (testosterone, androstendione, dehydroepiandrosterone and its sulfate), estrogens (estrone and estradiol) and progestins (progesterone and 17-hydroxyprogesterone). J Clin Endocrinol Metab 41: 556–562, 1975.