A Female Case of Kallmann's Syndrome

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Synopsis

A case of 20-year-old woman with hypogonadotropic hypogonadism and anosmia is reported, since very few female cases of Kallmann's syndrome have been reported so far in Japan. Three uncles on the father's side had no children. Height was 168 cm, and arm span 165 cm. The olfactory test revealed complete anosmia. Bone age was 13 year. Chromosome was 46 XX and normal karyotype. Basal levels of serum FSH, LH and estrogens (E1, E2 and E3) were low. Serum FSH and LH levels rose slightly only after LH-RH administration, and did not increase in clomiphene test. Plasma estrogens did not increase after daily injection of 150 IU of HMG for 3 successive days. The response of serum GH to arginine infusion was normal, while that to insulin-induced hypoglycemia was poor.

After the first description of patients with hypogonadism and anosmia in 1944 by Kallmann et al.(1944), deMorsier (1954) reported that such patients showed hypoplasia of hypothalamus and olfactory lobe from the autopsy findings. And this disorder has come to be called Kallmann's or deMorsier's syndrome as a clinical entity. Signs and symptoms in men are cryptorchidism, poor development of testis and penis, sparse or absent pubic and axillary hair, high voice and sometimes gynecomastia. Those in women are primary amenorrhea, small ovaries of which histological findings are like fetal, poor development of uterus, breast and sexual hair and deep voice. Cleft palate and color blindness are also other complications. Some authors reported deafness, synkinesia, mental retardation and renal deformity. There have been only few female patients of this syndrome in our country (Kondo et al., 1975). In this paper one female patient of Kallmann's syndrome is reported with special emphasis on the endocrinological studies.

Methods

Serum FSH, LH, TSH and GH were measured by the double-antibody method of radioimmunoassay, utilizing H-FSH Kit (Daiichi Radioisotope), H-LH Kit (Daiichi), HTSH Radioimmunoassay Kit (Daiichi) and GH RIA Kit (Dainabot). Standards for FSH and LH was Second IRP (International Reference Powder) and the minimum detectable levels of serum FSH and LH were 2 mIU/ml, respectively. Serum FSH in normal subjects in the follicular phase was 6 to 30 mIU/ml and serum LH 7 to 30 mIU/ml. Serum estrogen was determined by radioimmunoassay in which estrogens were fractionated by Sephadex LH20 column chromatography and B and F were separated by ammonium sulfate (Makino, 1974). Urinary estrogen was fractionated by alumina column chromatography and estrone, estradiol and estriol were determined by Brown-Kanbegawa's method (Kanbegawa, 1967).
Case Report

The patient, S. T., was a 20-year-old woman who was admitted to our Hospital for detailed examinations of primary amenorrhea and olfactory disturbance. She had visited a gynecologist because of amenorrhea at the age of 18 years and a low level of plasma gonadotropins was pointed out. After oral administration of estrogen for 6 months, the withdrawal genital bleeding occurred, but the cyclic period did not begin.

She was born on normal delivery when her mother was 37 years and father was 50 years of age. She showed normal growth and development until the age of 15 years except for the sense of smell. She had not been able to smell coffee, tobacco and odor of the lavatory room etc., even before she was pointed out to have sinusitis by a school doctor at 11 years of age. She had not suffered from serious diseases. She had average school achievements. She showed spurted growth from the height of 155 cm at the age of 15 years and gained 3 cm in height per year. She had not experienced headache, vomiting, visual disturbance, general fatigue and cold intolerance.

The family history revealed that 3 brothers of her father's had no children and one of them had smell disturbance with sinusitis. Mother was dead of ascites and jaundice at the age of 55 years. Father and her brother had no smell disturbance and no signs of hypogonadism and color blindness.

Her height was 168 cm, weight 50 kg and arm span 165 cm. She did not have deafness, color blindness, synkinesia or frontal deformity like hare-lip and cleft palate. Axillary and pubic hair was absent, and breast and subcutaneous adipose tissue showed poor development. She looked like a pre-adolescent girl. No abnormal findings were obtained concerning blood pressure, pulse, heart, lung and abdomen. The gynecological examinations showed the infantile external genitalia, small uterus and the adnexa without any findings. Basal body temperature appeared monophasic. Vaginal smear showed lack of superficial cells. There were no neurological abnormalities including visual fields, ocular fundi and sense of taste except olfactory disturbance.

Laboratory examinations: RBC 439 x 10^6/mm³, Hb 12.1 g/dl, Ht 36.1% and WBC 7,600/mm³ with normal differential counts. Liver function test was normal: GOT 22 U, GPT 18 U, ZTT 10.8 U, TTT 24 U, ChE 1.02 JpH, Alk-P 8 KAU and LDH 311 U/ml. Renal function test was as follows: urinalysis was normal, PSP test 41.4% (15 min) and serum creatinine 0.7 mg/dl. There were no remarkable changes in the intravenous pyelogram, the chest radiogram, ECG, ¹¹¹Te-brain scintigram and the audiometry. Sella turcica was normal in size and form. Bone age was 13 years with opened metaphysical line. Slightly slow waves were found in all leads of EEG. Buccal smear showed Barr bodies in 25% of cells and blood chromosome studies by the use of Giemsa banding indicated 46 XX normal karyotype.

Rhinological examination by the otologist was as follows: physical examination was normal, but the X-ray examination showed chronic sinusitis of the right maxilla and ethmoid. Olfactory threshold test indicated complete anosmia: she could not smell not only the odor of Alinamine intravenously injected but also each maximum concentration of ten sheets of odor paper such as β-phenyl ethyl alcohol, dl-camphor, exaltolid, γ-undecalactone, phenol, acetic acid, iso-valeric acid, cyclotene, scatole and diallyl sulfide determined by the Committee of the Ministry of Health and Welfare of Japan (Asaga, 1973).

Endocrinological study

Pituitary-gonadal system: Estrogens in the blood and urine were low (Table 1). Plasma FSH level was 2 mIU/ml and LH 3 mIU/ml 16 months before admission. We stimulated the secretion of gonadotropins by the intramuscular injection of 100 µg/day of LH-RH for 5 successive days. Serum FSH showed a slight increase on the second day of LH-RH administration, while serum LH increased on the fifth day after LH-RH injection was started (Fig. 1). After oral administration of clomiphene citrate (Clomid) at the dose of 100 mg/day for 5 days, serum FSH and LH did not increase (Fig. 2). By intramuscular injection of 150 IU/day of human meno-

<p>| Table 1. Urinary and plasma levels of estrogens |
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<th>µg/day</th>
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<td>E₁</td>
<td>0.96</td>
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<td>E₂</td>
<td>0.35</td>
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Fig. 1. LH-RH was injected intramuscularly at a dose of 100 µg/day for 5 days. LH showed a slight increase on the 5th day of LH-RH administration. FSH was not determined on the first day of LH-RH injection.
pausal urinary gonadotropin (HMG) for 3 days, plasma estrogens did not rise.

**Growth hormone:** Although serum GH increased from 4.8 to 16.9 ng/ml in response to 0.5 g/kg of body weight of arginine infusion for 30 min, it did not respond to the stimulation by intravenous injection of 0.1 U/kg of body weight of regular insulin which induced hypoglycemia lower than 50 mg/dl (Fig. 3).

**Pituitary-adrenal system:** 17-OHCS and 17-KS in the urine and serum cortisol were normal. In ACTH test in which 1.0 mg of Cortrosyn Z was injected every day for 3 days urinary 17-OHCS increased to 68.8 mg/day on the second day of stimulation from the basal level of 4.8 mg/day, and in metyrapone test in which metyrapone was administered orally at the dose of 3 g the normal response was observed.

**Pituitary-thyroid system:** BMR was -8.2%, T₄ 10.0 µg/dl and T₃-resin sponge uptake 25.2%. Thyroid scintigram was normal and ¹³I uptake was 19%. Serum TSH increased from 1.25 µU/ml to 12.8 µU/ml 30 min after the administration of 500 µg of TRH.

**Discussion**

According to Kallmann's report in 1944, one female and 11 male patients with hypogonadism and anosmia were found in 3 families. Agulhon et al. (1971) proposed that the masculine preponderance might be due to the transmission of the affection by the X chromosome. Although Jones et al. (1975) reported a female case of anosmia and hypogonadism with ovarian mosaicism (46 XX/47 XXY+), the chromosome study of the peripheral white blood cell in the present case was normal. In this syndrome both familial and non-familial cases have been described. There is a possibility that the case was familial because 3 of her uncles had infertility and one of them had anosmia.

The cause of smell disturbance in Kallmann's syndrome was ascribed to the poor development of olfactory lobe. A close relationship between olfactory and sexual functions has been proposed. Marshall and Henkin (1971) reported that several groups of patients with hypogonadism showed decreased olfactory acuity: the frequency of smell disturbance was high in the group...
of dysmenorrhea. However, the severe hyposmia was rather associated with oocyte in the ovaries and the slight hyposmia was demonstrated in subjects without oocyte. On the other hand, Hamilton et al. (1973) described in man that serum FSH and LH increased to clomiphene administration in subjects with subnormal olfactory responsiveness and that those did not respond in subjects with complete anosmia.

While disproportionately long extremities are the usual finding in isolated gonadotropin deficiency, the arm span was rather shorter than the height in the present case. Tagatz et al. (1970) exhibited 3 female cases of Kallmann’s syndrome whose arm span was longer than the height. One of them showed 7 cm longer, but the proportion was almost normal in other 2. Two male patients reported by Sparkes et al. (1968) appeared to have the abnormal proportion, and Hashimoto et al. (1973) reported one male patient of hypothalamic hypogonadism who showed almost normal proportion. It is probable that GH, sex hormone and other hormones may influence the growth of the height and extremities.

Following the administration of 100 µg/day of LH-RH for 4 successive days, serum LH level increased slightly at 30 min after the intramuscular injection of 100 µg of LH-RH and the release of gonadotropins was not evoked after administration of 100 mg of clomiphene for 5 successive days in the present case. This fact may suggest that the primary lesion is located in the hypothalamus (Zárate et al., 1974). Boyar (1969) reported the effect by the larger doses of clomiphene in stimulating the secretion of gonadotropins, but Schroffner and Furth (1970) demonstrated that clomiphene was ineffective even at higher doses. While the administration of HMG did not change the plasma estrogen level, Boyar et al. (1973) considered that the chronic understimulation of gonadal organs by the low levels of gonadotropins may lead to the unresponsiveness of the target tissue to the exogenous gonadotropins. Generally, patients with this syndrome do not show any response to clomiphene but show the slight increase to HMG and HCG.

Another abnormal endocrinological finding was that serum GH did not respond to insulin-induced hypoglycemia. Demura et al. (1972) reported one male of Kallmann's syndrome in whom GH did not respond to arginine. Boyar et al. (1973) also exhibited that one male of hypogonadotropic hypogonadism and anosmia showed poor response of GH to insulin-induced hypoglycemia and arginine infusion, but in another male the response was good. Although the mechanism of dissociation in the present case is unknown, hypogonadism may have been related to the poor response of GH to insulin-induced hypoglycemia. A close relationship between sex hormone and GH has been noticed. Martin et al. (1968) demonstrated that the administration of testosterone to normal immature males at the dose of 25 mg/day for 5 days resulted in the recovery of the impaired secretion of GH by the insulin-induced hypoglycemia. As to the effect of estrogen on GH secretion, Franz et al. (1965) postulated that the estrogens act to enhance the pituitary sensitivity to the GH releasing effects of physical activity. Low levels of estrogens in the present case may be related to the poor response of GH to hypoglycemia. The impaired site of GH secretion may be located in the hypothalamus in the present case.

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