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A MALE CASE OF KALLMANN'S SYNDROME : FERTILITY INDUCED BY GONADOTROPIN (hCG/hMG) THERAPY

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Abstract : A 24-year-old male patient with Kallmann's syndrome who fathered two children after gonadotropin therapy is reported here. He was diagnosed with Kallmann's syndrome because of hypothalamic hypogonadism associated with anosmia. The gonadotropin therapy was initiated which involved treatment with human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG). After 3 years of treatment, his secondary sexual characteristics developed to near the adult level and sperm were detected in his semen. Although pulsatile luteinizing hormone releasing hormone (LH-RH) injection using a mini-pump was tried for 4 months, it did not maintain the plasma testosterone at normal levels. At 29 y the patient was switched to gonadotropin therapy. His sperm count reached $6\times10^6/mm^3$, and his wife became pregnant ; they had a female baby. His second child was born when the patient was 32 y. The sequence of the *KAL* gene was normal in all 14 exons of the patient's DNA. Here we describe the clinical benefits of gonadotropin therapy and LH-RH therapy.

Index Terms

Kallmann's syndrome, hypogonadotropic hypogonadism, gonadotropin therapy, pulsatile LH-RH therapy, *KAL* gene

Kallmann's syndrome is characterized by hypogonadism and anosmia, and is caused by a defect in migration and targeting of gonadotropin-releasing hormone (Gn-RH)-secreting neurons and olfactory neurons during embryonic development. In 1944, Kallmann et al[1] described 12 related patients from 3 pedigrees and showed the existence of an X-chromosome-linked form. Following their study, many cases were reported, and that three modes of transmission, X-linked recessive, autosomal recessive and autosomal dominant exist ; sporadic cases have also been described[2]. In 1989, Ballabio et al.[3] and Petit et al.[4] independently isolated the *KAL* by positional cloning of X-linked cases. Mutation of *KAL* is recognized as one possible of recessive X-linked Kallmann's syndrome[5]. Gonadotropin therapy[6,7] and LH-RH injection[8,9] have been effective in treating Kallmann's syndrome, but which therapy is most effective in stimulating fertility is controversial[10]. In this study, we compared plasma testosterone levels after treatment with each type of therapy and checked for mutation in the *KAL* gene.

CASE REPORT

A 24-year-old man was referred to our hospital in September, 1990, because of his failure to develop secondary sexual characteristics. He was born at full term with a normal delivery. His

growth and mental development were normal in childhood. His parents noticed that he could not smell anything. At 12 years of age, the patient recognized that his penis was small, and he could not feel testicles in his scrotum. He underwent surgery for bilateral cryptorchidism at 15 y. Gonadotropin therapy was started, and pubic hair, voice change, and ejaculation were observed. The patient ceased gonadotropin therapy after 3 y because he thought his secondary sexual characteristics would complete their development spontaneously.

When his secondary sexual characteristics did not continue to develop, he was referred to our hospital. His height was 169 cm and body weight was 51.0 kg. Arm span was 167 cm. Facial appearance was feminine and a mustache was absent. No gynecomastia was found. Pubic hair developed to Tanner stage II. His penis length was 3.2 cm. The right and left testes were both 3.0 ml in volume. No dyschromatopsia was found. He could not recognize any smells. No neurological abnormalities were found.

Basal hormone values (Table 1) : Plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were low (<0.5 mIU/ml and 1.0 mIU/ml, respectively). Testoster-

Table 1. Basal hormone values

		normal range			normal renge
			Cortisol	22.6 μg/dl	(4.3~10.7)
ACTH	26.9 pg/ml	(4.4~48.0)	IGF-I	1.2 IU/ml	(1.0~1.5)
GH	7.5 ng/ml	(<2.3)	T_3	162.2 ng/ml	(80~200)
PRL	5.4 ng/ml	(<15)	T_4	11.3 ng/ml	(4.5~12.0)
TSH	0.6 μU/ml	(0.4~5.0)	Free T_4	1.3 ng/ml	(0.9~1.8)
LH	<0.5 mIU/ml	(1.5~5.2)	Testosterone	0.8 ng/ml	(2.7~10.7)
FSH	1.0 mIU/ml	(2.9~8.2)	E_2	<25 pg/ml	(15~60)

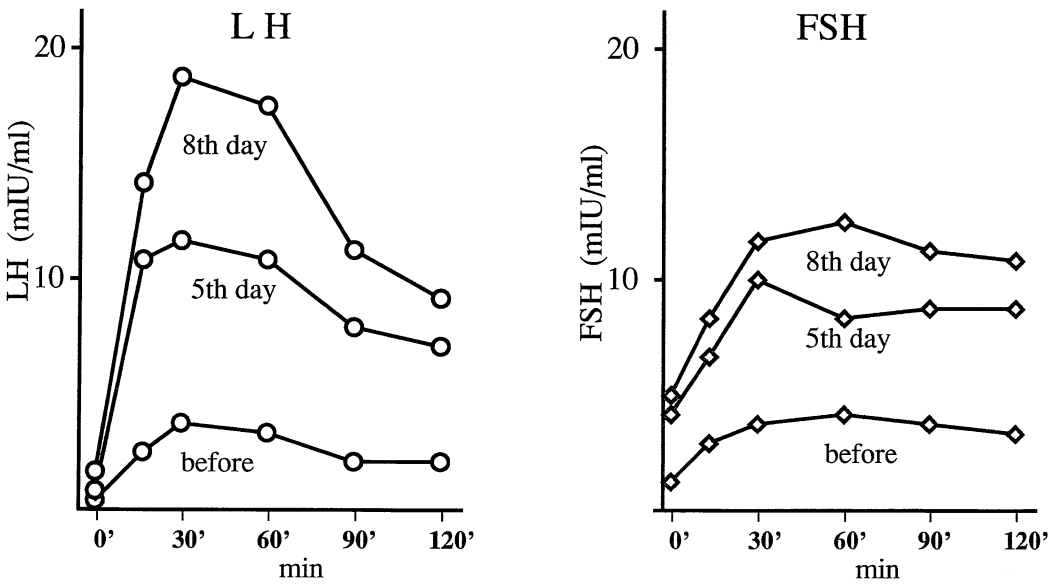

Fig. 1. Consecutive LH-RH provocation test : Stepwise elevation of LH and FSH levels were found after consecutive LH-RH loading.

one was 0.8 ng/ml and estradiol (E_2) was below the detectable level (<25 pg/ml). Other basal values of pituiary hormones were within normal ranges.

Consecutive LH-RH test (Fig. 1) and chromiphen test: Secretion of plasma LH and FSH was stimulated stepwise by administration of LH-RH. Chromiphen test was negative for secretion of LH and FSH.

Pituitary function test (Table 2): Insulin tolerance test showed that plasma corticotropin (ACTH), cortisol, and growth hormone (GH) were paradoxically reduced by hypoglycemia (glucose below 50 mg/dl). Other GH provocation tests, the arginine test, glucagon-propranolol test and growth hormone releasing hormone (GRH) test, showed normal GH responses. TSH secretion responded normally to TRH stimulation.

These pituitary function tests indicated that this patient had hypogonadotropic hypogonadism of hypothalamic origin, and he was subesequently diagnosed with Kallmann's syndrome because of the anosmia.

Clinical course (Fig. 2): Gonadotropin therapy, HCG 5000 units×2/week and HMG 75 units, 1×/week, was initiated. After 6 months, testosterone enantate, 125 mg/2 weeks, was added to stabilize testosterone levels. Although his sperm count was low for 2 years of therapy, at 2.5 years sperm levels reached as $3\times10^6/mm^3$. After 3 years of gonadotropin therapy, the treatment was switched to pulsatile LH-RH subcutaneous infusion by mini-pump. LH-RH therapy did not maintain normal testosterone levels. During LH-RH therapy, plasma LH and FSH basal levels were low, and no pulsatile secretion was observed. For comparison, plasma

Table 2. Pituitary function tests

1) ITT (insulin tolerance test)

	min	Bf.	10'	20'	30'	40'	50'	60'
B. glucose	(mg/dl)	101	82	55	47	47	51	88
ACTH	(pg/ml)	19.2	19.6	16.2	13.5	13.0	17.0	15.0
Cortisol	(μg/dl)	9.7	7.7	6.6	6.4	5.7	5.4	5.2
GH	(ng/ml)	2.1	1.1	0.9	0.9	1.0	0.9	0.7

2) Arginin test

	min	Bf.	30'	60'	90'	120'
GH	(ng/ml)	8.4	14.5	13.1	9.3	14.2

3) Glucagon-Propranolol test

	min	Bf.	15'	30'	60'	90'	120'	150'	180'
GH	(ng/ml)	5.4	4.7	1.9	1.1	2.5	4.8	22.2	21.8

4) GRH test

	min	Bf.	15'	30'	60'	90'	120'
GH	(ng/ml)	4.5	33.6	39.2	31.8	20.9	7.1

5) TRH test

	min	Bf.	15'	30'	60'	90'	120'
TSH	(μU/ml)	0.6	3.9	5.2	4.2	3.0	2.2
PRL	(ng/ml)	8.2	26.0	26.9	19.2	11.2	10.6

LH and FSH levels during pulsatile LH-RH infusion were examined in two other patients with hypothalamic hypogonadism and one normal volunteer. The LH and FSH secretion patterns of the other cases and even of the normal volunteer did not show the normal spiky pattern (Fig. 3). We concluded that pulsatile LH-RH infusion was not effective for this patient, and changed to gonadotropin therapy with an increased dose of HMG, 150 units×2 times/week. After 4 years of therapy, his wife became pregnant and delivered a normal, healthy female infant. Two years after the first birth, his wife became pregnant and delivered a healthy male infant.

Plasma ACTH, cortisol, and GH responses to the insulin tolerance test were normal after gonadotropin therapy. For comparison, plasma GH response to the insulin tolerance test was examined in other three individuals with Kallmann's syndrome ; the peak levels of GH were low but improved after gonadotropin therapy (Fig. 4).

DISCUSSION

The Kallmann's syndrome patient reported here had gonadotropin therapy for 3 years after undergoing surgery for bilateral cryptorchidism at age 15. The gonadotropin therapy was resumed at age 24 when Kallmann's syndrome was diagnosed. This patient fathered two children while receiving gonadotropin therapy. Treatment for Kallmann's syndrome should address the following problems :

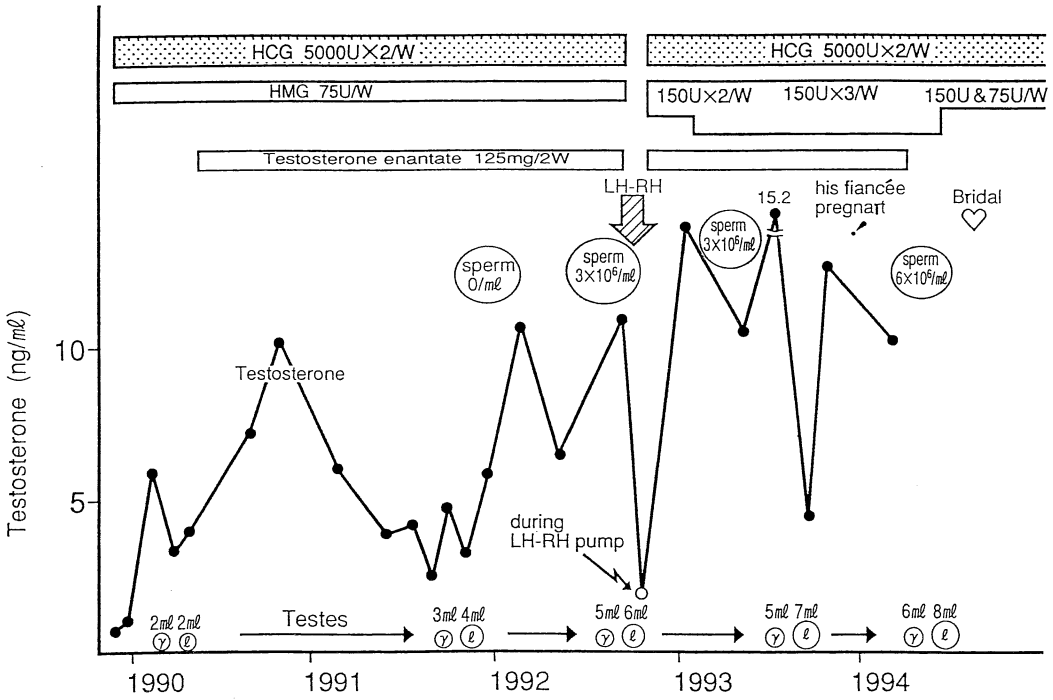

Fig. 2. Clinical course and testosterone levels compared during gonadotropin therapy and LH-RH therapy

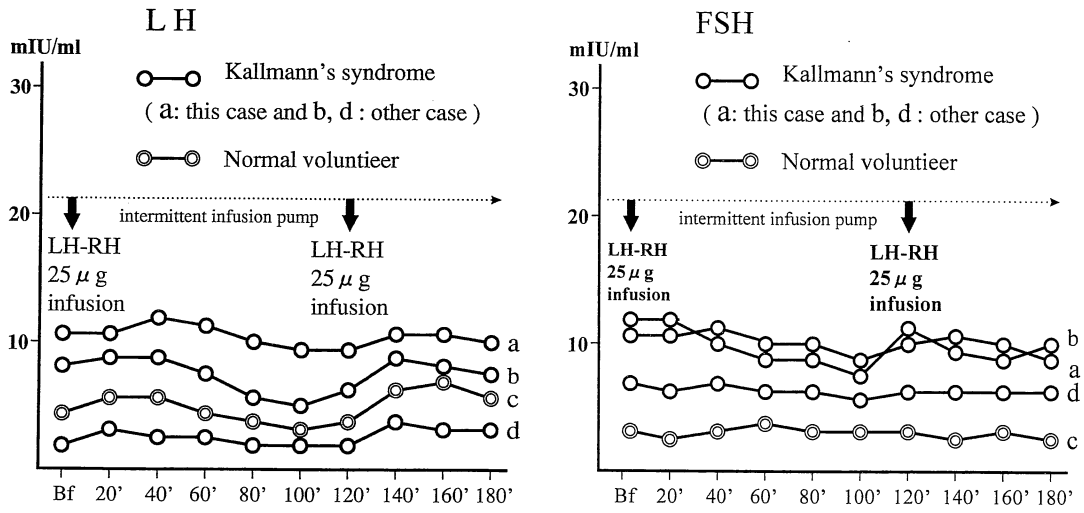

Fig. 3. LH and FSH secretion pattern of this patient (a), other kallmann's syndrome (b and d) and normal volunteer (c) during intermittent LH-RH injection.

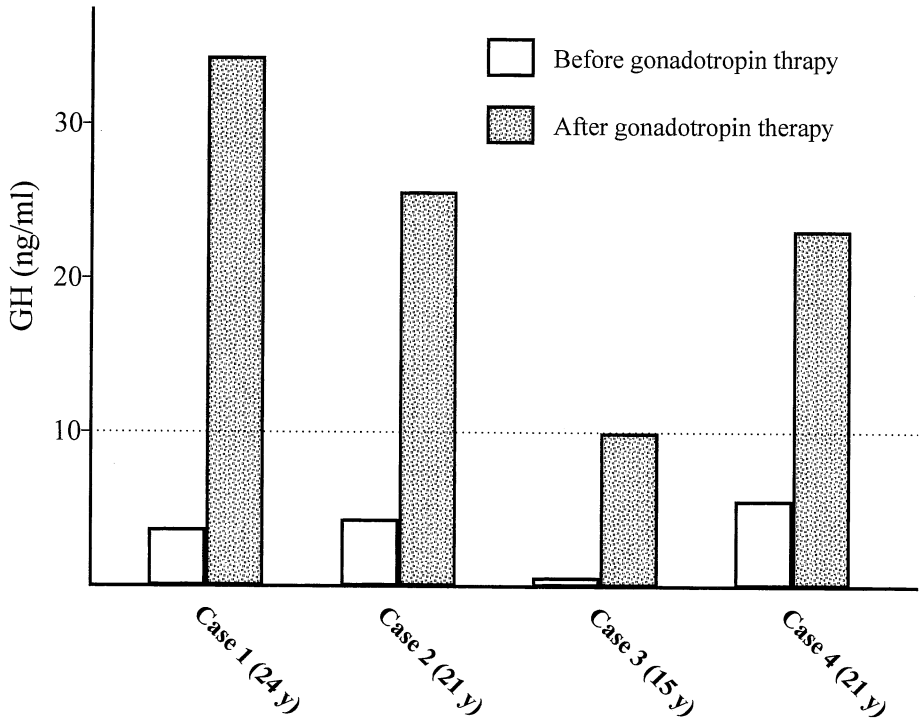

Fig. 4. The GH responses to insulin tolerance test: before and after gonadotropin therapy. Case 1 shows this patient and case 2 to 4 shows other patients of Kallmann's syndreme.

1) Reduced spermatogenesis and infertility due to delays in initiating treatment.
2) Inferiority complex because without hormone therapy patients fail to develop normal sexual characheristics.
3) Whether gonadotropin or LH-RH therapy is most effective for treating Kallmann's syndrome.

With respect to infertility, this patient had aspermia but spermatogenesis improved after 3 y of gonadotropin treatment. Spermatogenesis was not observed in a different patient with Kallmann's syndrome aged 35 y, who was treated with gonadotropin and LH-RH therapy for 8 y. We speculate that the initial gonadotropin therapy of this patient at age 15 y played an important role in spermatogenesis. It is possible that early treatment is necessary for spermatogenesis.

Most individuals with hypogonadism have inferiority complexes because they fail to develop normal sexual characteristics without hormone therapy. Huisman et al.[11,12] reported that hypogonadotropic hypogonadism patients had difficulties with independence and identity development. Because the patients who delay starting therapy have strong inferiority complexes, they sometimes do not marry even after therapy results in normal sexual development. Ideally, the therapy would be started near puberty and would stimulate normal sexual development. For this reason, early diagnosis is essential.

The relative effectiveness of gonadotropin therapy and LH-RH therapy is still controversial. Kliesch et al.[13] treated twenty-six men with either hypothalamic (idiopathic hypogonadotropic hypogonadism, n=6 : Kallmann syndrome, n=8), or pituitary disorders (n=12) with gonadotropin and pulsatile LH-RH and compared their effects. They concluded that both gonadotropin and pulsatile LH-RH theraphy are effective in stimulating spermatogenesis and fertility in hypogonadotropic hypogonadal men, despite maldescended testes, low initial testicular volumes or sperm concentrations below the normal limit.

Theoretically, pulsatile LH-RH infusion therapy should more effective for treatment of hypothalamic hypogonadism, but it is difficult to imitate the normal LH and FSH secretion patterns, because the therapy is via subcutaneous infusion. Some reported patients gained fertility after LH-RH therapy[8,9,14], however, this therapy was ineffective for our patient. These differences may result from variation in gonadotroph cell responses to LH-RH and the genetic and phenotypic heterogeneity of this disease. Gonadotropin therapy is easily continued and normal testosterone levels are easily maintained, and therefore gonadotropin therapy is not inferior to LH-RH therapy.

How do we recognize the paradoxical GH response to insulin tolerance test before gonadotropin therapy? In three other patients with Kallmann's syndrome, the same non-response to insulin tolerance test before therapy and normal response after therapy were found. We speculate that the GH secretion by hypoglycemia is enhanced by gonadotropin therapy or testosterone secretion during sexual development.

Using a direct sequence method, we analyzed all 14 exons of *KAL* but found no mutations. There are three possible explanations for Kallmann's syndrome that does not result from a mutation in *KAL* : 1) an alternative mode of inheritance (e. g. non-X-linked recessive) ; 2) a mutation in the noncoding portions of Exon 1 or Exon 14 ; or 3) a mutation in the promoter region or an intron.

Finally, hormonal therapy alone is not sufficient for hypogonadism patients. Psychological care for the patient's inferiority complex should be included. We established a support group with this patient and his mother for consultation with other patients. This case is an important model of gonadotropin therapy and psychological care for a patient with Kallmann's syndrome.

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