

# Markedly Delayed Puberty or Kallmann's Syndrome Variant

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**A diagnosis of Kallmann's syndrome was made in a 25-year-old man. After 21 months of treatment with parenteral T, spontaneous puberty occurred at the age of 27.**

**Key words:** Kallmann's syndrome variant, delayed puberty.

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Kallmann's syndrome is characterized by anosmia or hyposmia and idiopathic hypogonadotropic hypogonadism, presumably due to simultaneous failure of development of both the olfactory tracts and the medial basal hypothalamus, which controls the secretion of gonadotropin releasing hormone (GnRH) (Knobil and Plant, 1978; Bardin and Paulsen, 1981). Since an intact olfactory mechanism plays an important role in reproduction in other species (Parkes and Bruce, 1961; Wilson and Bossert, 1963; Meinwald et al, 1966), it is not surprising that in man a defect in the ability to smell also may be associated with impaired reproduction. This disorder may be transmitted as an x-linked or as an autosomal inheritance (Goldstein and Motulsky, 1981, Lieblich et al, 1982). Additional abnormalities, such as a cleft lip and palate, facial asymmetry and other skeletal deformities, renal agenesis, vascular anomalies, and congenital deafness, are found in a significant number of cases (Lieblich et al, 1982).

Minimal to complete expression may be found in members of the same family (Bardin and Paulsen, 1981; Lieblich et al, 1982). Relatives of patients with both anosmia and idiopathic hypogonadotropic hypogonadism (complete Kallmann's syndrome) may have either anosmia or isolated gonadotropin deficiency (Santen and Paulsen, 1973; Weinstein and Reitz,

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1974; Rosen et al, 1979; Lieblich et al, 1982). Since there are so many associated congenital somatic defects, as well as presumed quantitative differences in GnRH secretion (Lieblich et al, 1982, Barkan et al, 1985), there is thus considerable heterogeneity in Kallmann's syndrome.

Rezvani et al (1975) reported a boy with anosmia, who presented with idiopathic hypogonadotropic hypogonadism at the age of 17 1/2 years, in whom puberty occurred spontaneously at the age of 20 3/4 years. Whether this was simply late development in a subject with an olfactory deficiency or a variant of Kallmann's syndrome is unclear. The patient in this report, who satisfied the criteria for Kallmann's syndrome, underwent spontaneous sexual maturation at the age of 27.

## Case Report

In October, 1972 a 25-year-old man presented because he had never developed sexually. At ten years of age, an orchiopexy was performed for an undescended right testis. At fifteen, axillary and pubic hair appeared but there were no other secondary sexual changes. Subsequently, erections and ejaculations of opalescent fluid occasionally occurred. There was no history of head injury, central nervous system infection, headache, visual symptoms, gynecomastia or galactorrhea. He remained self-conscious about his lack of masculine development, and had also been aware of his limited ability to detect odors. No objective tests had ever been done. There were no urinary symptoms or eye-muscle problems. He was

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an only child and was unaware of any similar problems in his family.

Physical examination revealed a well-nourished, moderately obese man. Facial asymmetry was present, with the left side fuller than the flatter right side. The patient weighed 203 lb, was 180.5 cm in height with an arm span of 182 cm, crown to symphysis 86 cm, and symphysis to floor of 94.5 cm. There was no beard or facial acne. The flaccid penis was 3.75 cm in length, the testes 2.5 cm in longest diameter, and the prostate was not palpable. The concentration of serum T was 50 ng/dl (normal 200–1100 ng/dl), LH\* was 0.6 ng/ml (normal 0.2–4), FSH† was 3.5 ng/dl (normal 0.2–5), appropriately low for a prepubertal male.

A diagnosis of idiopathic hypogonadotropic hypogonadism was made, and testosterone enanthate, 200 mg intramuscularly, was administered every 1 to 3 weeks, with the development of secondary sexual characteristics, i.e. beard, acne, deepening of the voice, enlargement of the penis, and appropriate scrotal changes. T therapy was continued from November 1972 to January 1975, at which time definite growth of the testes was noted, with the left testis measuring 4.5 × 2.5 cm and the right testis, probably injured during orchiopexy, 3 × 2.5 cm.

After T had been discontinued for two months, two GnRH studies‡ were performed (Weitzman et al, 1975), one while the subject was awake and the other while asleep, using an intravenous bolus of 100 µg of GnRH, collecting blood every 15 minutes for the first hour and every 30 minutes for an additional three hours. The baseline value for LH was 15 mIU/ml, peaking at 67.3 mIU/ml while awake and 51.8 mIU/ml while asleep; the baseline value was 19.5 mIU/ml for FSH, peaking at 43.5 mIU/ml while awake and 40 mIU/ml during sleep. LH and FSH baseline and response to GnRH were normal for an adult male (Roth et al, 1973, Wollensen et al, 1976). Endogenous T was normal at 741 ng/dl. A sperm count was 46 × 10<sup>6</sup> in a volume of 1.5 ml.

Severe hyposmia was confirmed in May, 1975. The patient failed to smell nitrobenzene at a concentration of less than 10<sup>-2</sup> M (normal 10<sup>-6</sup> to 10<sup>-3</sup> M) and pyridine in concentration of less than 1 M (normal 10<sup>-7</sup> to 10<sup>-3</sup> M) (Rosen et al, 1979, Henkin and Bartter, 1966).

\*LH standard first IRP-HMP (WHO-MRC) 69/104.

†FSH standard second IRP-HMG.

‡Normal baseline values for LH and FSH for a normal adult male are 3–20 mIU/ml and 2–15 mIU/ml, respectively. A normal response to a bolus of 100 µg GnRH is at least twice the baseline for LH and FSH.

He was re-evaluated in March, 1982. Since 1975, the patient had shaved daily and had sexual intercourse occasionally. He had noted that at times his skin had been oilier and he had more acne than previously. Because of a professed lack of self-control, he had eaten a great deal and weighed 350 lb. The left testis measured 6 × 4.5 cm, the right testis, 4 × 2.5 cm. Both lobes of the prostate were palpable and normal. Hair distribution was normal male in character. A random serum disclosed a T of 300 ng/dl, an LH of 10.3 mIU/ml, and FSH of 19.6 mIU/ml.

### Discussion

The patient of Rezvani et al (1975) was 20 3/4 years old when puberty occurred, but this patient was 27, well beyond the range of delayed puberty. The olfactory deficit was documented as sexual development proceeded normally. A significant sperm count confirmed the completeness of spontaneous sexual development. Both Leydig and germinal cells matured normally despite and during the administration of T therapy.

This patient had facial asymmetry and hyposmia. Hypogonadotropic hypogonadism was supported by the lack of secondary sexual characteristics, including a high-pitched voice, absence of body and facial hair, eunuchoid habitus, small penis and testes, and inappropriately low gonadotropin in the presence of a low T level in a 25-year-old man.

Exogenous testosterone therapy induced desired changes in voice, hair distribution, libido, and sexual performance, but did not inhibit spontaneous sexual development. The patient had a sperm count of 46 × 10<sup>6</sup> and endogenous T was 741 ng/dl. That sexual maturation was complete was further verified by normal adult responses to GnRH. Although the idiopathic hypogonadotropic hypogonadism of Kallmann's syndrome previously has been regarded as permanent, the patient had a much delayed but completely normal puberty.

This report indicates that a subject with all the laboratory and clinical criteria of Kallmann's syndrome need not be committed to lifelong T therapy, since a simple clinical observation of testicular enlargement during the course of therapy may be all the evidence necessary to indicate the spontaneous onset of a very delayed puberty. Recent work has been very encouraging for both male (Hoffman and Crowley, 1982; Finkel et al. 1985) and female (Santoro et al, 1985) human subjects with idiopathic hypogonadotropic hypogonadism. Using low-dose pulsatile subcutaneous injections of GnRH, Hoffmann and Crow-

ley (1982) induced puberty in men with idiopathic hypogonadotropic hypogonadism. Gonadotropin and T levels were increased within a few weeks. Spermatogenesis, when it occurred, required 43 weeks, a short period of time compared with spontaneous puberty in normal subjects, which evolves over a period of years. Puberty with spermatogenesis has been uniformly induced in idiopathic hypogonadotropic hypogonadism with hCG and hMG (Finkel et al, 1985). In the presence of unilateral cryptorchidism, even following orchiopexy, spermatogenesis occurred in only one of seven subjects. Impaired fertility can be explained by histologic damage in both the cryptorchid and the noncryptorchid testes (Mengel et al, 1974), leading to elevations of FSH and LH (Lipshultz et al, 1976; Werder et al, 1976).

In the mouse model with congenital idiopathic hypogonadotropic hypogonadism due to GnRH deficiency, hypogonadism may be reversed with transplantation of normal fetal hypothalamic tissue (Krieger et al, 1982). Although clomiphene citrate (Boyar, 1969) has been reported to stimulate gonadotropin over a 32-day period, this has been the exception and not the rule.

In humans, there appears to be a heterogeneity of idiopathic hypogonadotropic hypogonadism (Lieblich et al, 1982, Barkan et al, 1985). Barkan et al (1985) subdivided such subjects into two groups based on the presence or absence of spontaneous LH pulsations over a 24-hour period. The group with no LH pulses was regarded as totally deficient in GnRH, whereas the other group was regarded as partially deficient. When exogenous GnRH was given initially, only FSH increased in the totally deficient group, whereas FSH, LH, and T increased in the partially deficient group and both groups exhibited significant rises in gonadotropin. Boyar et al (1976) noted the difference between subjects with idiopathic hypogonadotropic hypogonadism both clinically (i.e., testicular size), histologically, and by plasma concentration of gonadotropin and T. Men with no spontaneous pulsations of LH during sleep or while awake were completely prepubertal both histologically and by hormone analysis. Those with spontaneous pulsations had testicular maturation and higher concentrations of gonadotropin and T. A spectrum of subjects with hypogonadotropic hypogonadism was thus demonstrated.

The heterogeneity of this disease appears to be due to quantitative differences in GnRH secretion (Boyar et al, 1976; Barkan et al, 1985). Complete absence of GnRH is expressed clinically by no testicular or pub-

ertal development and by the complete absence of any spontaneous LH, FSH, and T pulsations over a 24-hour period. As GnRH secretion increases in idiopathic hypogonadotropic hypogonadism, so does testicular size, although not to normal dimensions, as well as increases in the frequency, amplitude, and duration of spontaneous pulsations of LH, FSH, and T, first during sleep and finally, around-the-clock, as in normal postpubertal men (Weitzman et al, 1975; Boyar et al, 1976). For normal puberty, GnRH must be secreted in a pulsatile fashion since continuous administration suppresses gonadotropin release (Belchetz et al, 1978; Widt et al 1980). Successful induction of puberty aims at simulating the normal pulsatile release of GnRH in all respects.

Although it is now feasible to induce puberty with spermatogenesis in subjects with idiopathic hypogonadotropic hypogonadism, a review of the literature has failed to disclose any other case of spontaneous puberty in a subject in his twenties with Kallmann's syndrome.

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### Reproduction and Human Cancer

The National Cancer Institute and the National Institute of Child Health and Human Development are sponsoring an International Conference on Reproduction and Human Cancer in Bethesda, Maryland, May 11-13, 1987, to focus on the effects of cancer and its treatment on reproduction, including possible genetic effects. Poster sessions are planned to accommodate offered papers. Contact: Drs. John J. Mulvihill (Landow Building, Room 8C41) or Richard J. Sherins (Building 10, Room 10N234), National Institutes of Health, Bethesda, Maryland 20892, or Mary E. Clark, (Conference Manager). Telephone: (301) 589-6760.

### 11th International Congress on Animal Reproduction and Artificial Insemination

The 11th International Congress on Animal Reproduction and Artificial Insemination will be held at University College Dublin, from June 26-July 1, 1988. Plenary session topics will include neuroendocrine control of reproduction, gene transfer/embryo manipulation in animal production, establishment of pregnancy. In addition, there will be several symposia relating to many areas of animal reproduction. Contact:

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