ADULT-ONSET IDIOPATHIC HYPOGONADOTROPIC HYPOGONADISM — A TREATABLE FORM OF MALE INFERTILITY

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ABSTRACT

Background Men with isolated gonadotropin-releasing hormone (GnRH) deficiency typically present with an absence of pubertal development. We describe an adult-onset form of idiopathic hypogonadotropic hypogonadism that develops after puberty.

Methods We studied 10 men (age, 27 to 57 years) with normal sexual maturation, idiopathic infertility, sexual dysfunction, low serum testosterone concentrations, and apulsatile secretion of luteinizing hormone on frequent blood sampling. All the men had otherwise normal anterior pituitary hormone secretion and sellar anatomy. We compared the results of semen analyses and measurements of testicular volume, serum testosterone, inhibin B, and gonadotropins in these men with the results in 24 men with classic GnRH deficiency before and during GnRH-replacement therapy and in 29 normal men of similar age.

Results Serum gonadotropin concentrations in the men with adult-onset GnRH deficiency were similar before and during pulsatile GnRH administration to those in the men with classic GnRH deficiency. However, as compared with men with classic GnRH deficiency, men with adult-onset hypogonadotropic hypogonadism had larger mean (±SD) testicular volumes (18±5 vs. 3±2 ml, $P<0.001$), serum testosterone concentrations (78±34 vs. 49±20 ng per deciliter [2.7±1.2 vs. 1.7±0.7 nmol per liter], $P=0.004$), and serum inhibin B concentrations (119±52 vs. 60±21 pg per milliliter, $P<0.001$). Treatment with GnRH reversed the hypogonadism and restored fertility in each of the five men who received long-term therapy.

Conclusions The recognition of adult-onset hypogonadotropic hypogonadism in men as a distinct disorder expands the spectrum of GnRH deficiency and identifies a treatable form of male infertility. (N Engl J Med 1997;336:410-5.)

MEN with idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome (idiopathic hypogonadotropic hypogonadism and anosmia) have severe gonadotropin-releasing hormone (GnRH) deficiency.[1,2] Typically, men with either form of isolated GnRH deficiency have no pubertal development and respond to treatment with exogenous, pulsatile GnRH, thus localizing their defect to the hypothalamus rather than the pituitary.[2-4] There are variations in both the severity and time of onset of GnRH deficiency.[5-7] Classic isolated GnRH deficiency (Kallmann's syndrome and idiopathic hypogonadotropic hypogonadism) is congenital. When the presentation includes cryptorchidism and microphallus, GnRH secretion is presumed to have been absent during midgestation.[8] A less well characterized group includes men who had an age-appropriate, normal puberty but in whom GnRH deficiency subsequently developed without an identifiable cause.

This study was done to characterize the clinical and biochemical features of this latter group. Because sexual dysfunction and decreased libido are symptoms that often escape medical attention, the men we studied had symptomatic hypogonadism for many years before diagnosis. In half of them the disease was ultimately identified only through infertility evaluations, despite prior reports of impotence, loss of strength, and fatigue. A greater awareness of this syndrome may lead to earlier diagnosis and treatment.

METHODS

Study Subjects

Men with Adult-Onset Idiopathic Hypogonadotropic Hypogonadism

We studied 10 men (age, 27 to 57 years) given a diagnosis of adult-onset idiopathic hypogonadotropic hypogonadism on the basis of the following: completion of puberty by the age of 18 years; presence of erectile function and ejaculation or nocturnal emissions; appearance of facial hair and libido; subsequent development of hypogonadism, including loss of sexual function, decreased libido, or infertility; repeated serum testosterone values below 100 ng per deciliter (3.47 nmol per liter) accompanied by low or normal serum luteinizing hormone and follicle-stimulating hormone concentrations; normal serum ferritin concentrations; normal base-line serum thyroxine concentrations and normal responses of serum thyrotropin, prolactin, growth hormone, and cortisol to thyrotropin-releasing hormone and insulin-induced hypoglycemia; normal findings on radiographic imaging of the hypothalamic–pituitary region; and an apulsatile pattern of luteinizing hormone secretion. These men were identified from a group of over 150 men referred to the Reproductive Endocrine Unit at Massachusetts General Hospital for evaluation of hypogonadotropic hypogonadism. Because *Kal* gene mutations are rare in men with the sporadic form of Kallmann's syndrome,[9] the probability of finding such a mutation in a man with adult-onset hypogonadotropic hypogonadism is very low. Therefore, the men were not tested for mutations of the *Kal* gene.

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Men with Classic GnRH Deficiency

Twenty-four men (age, 18 to 58 years) who repeatedly had serum testosterone values below 100 ng per deciliter (3.47 nmol per liter) accompanied by low or normal serum luteinizing hormone and follicle-stimulating hormone concentrations; normal serum ferritin concentrations; normal base-line serum thyroxine concentrations and normal responses of serum thyrotropin, prolactin, growth hormone, and cortisol to thyrotropin-releasing hormone and insulin-induced hypoglycemia; normal findings on radiographic imaging of the hypothalamic–pituitary region; and an apulsatile pattern of luteinizing hormone secretion, but who had no evidence of spontaneous pubertal development were classified as having classic GnRH deficiency and served as one control group. The results of detailed biochemical studies in these men have been reported previously.[4,7]

Normal Men

Twenty-nine normal men (age, 18 to 37 years) who met previously described selection criteria[7] provided normative data for serum reproductive hormone concentrations.

All studies were approved by the Human Studies Committee of Massachusetts General Hospital. All men provided informed consent for these studies and for the administration of GnRH.

Protocol

Testicular volume was measured with a Prader orchidometer. Serum luteinizing hormone and follicle-stimulating hormone were measured in blood samples obtained every 10 minutes for a period of 12 to 24 hours. Serum testosterone, inhibin B, and estradiol were measured in pooled aliquots of equal volumes of these samples. All hormones were measured as previously described.[10-12]

GnRH was synthesized at the Salk Institute and made available by the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development. GnRH was administered subcutaneously by a portable mini-infusion pump every two hours for at least six months in 5 of the men with adult-onset idiopathic hypogonadotropic hypogonadism and all 24 of the men with classic GnRH deficiency. The doses were individualized to maintain serum luteinizing hormone concentrations in the mid-normal range for men, as previously described.[4] Three men with adult-onset disease received GnRH for less than three months, and the other two men in the group did not receive GnRH. One received treatment with human chorionic gonadotropin, and the other with testosterone. During the period of GnRH administration, serum luteinizing hormone, follicle-stimulating hormone, and testosterone were measured at least once a month in pooled serum from blood samples obtained at 10-minute intervals for 2 to 12 hours, and semen analyses were performed periodically.

Statistical Analysis

When the values were distributed normally, data for the three groups were compared by two-tailed t-tests. When the values were not distributed normally, nonparametric analysis was used. The results are expressed as means ±SD unless otherwise stated.

RESULTS

Base-Line Characteristics

The mean (±SD) age of the 10 men with adult-onset hypogonadotropic hypogonadism at presentation was 35±10 years (Table 1), and their symptoms had been present for a mean of 5±4 years (range, 1 to 11). The presenting symptoms were decreased libido, impotence, and idiopathic infertility (Table 1). Four men reported previous paternity, and none had a history of tumor, exposure to radiation, infection, or infiltrative disease involving the pituitary or hypothalamic regions. All had normal body-mass-index values, dietary habits, and exercise patterns. Their histories of head trauma, prior medical illness, psychiatric disorders, medication use, alcohol abuse, and illicit-drug use, although of unclear importance, are summarized in Table 1. All had a normal sense of smell. None had features associated with congenital GnRH deficiency (midline facial defects, synkinesis, or a family history of GnRH deficiency or anosmia).[13] Six men had no cranial abnormalities on computed to-

TABLE 1. CLINICAL AND RADIOGRAPHIC CHARACTERISTICS OF 10 MEN WITH ADULT-ONSET HYPOGONADOTROPIC HYPOGONADISM.

PATIENT NO.	CHIEF SYMPTOM AT PRESENTATION	AGE AT DIAGNOSIS (YR)	PRIOR PATERNITY	MEDICAL HISTORY	USE OF MEDICATIONS, ALCOHOL, AND ILLICIT DRUGS	CRANIAL-IMAGING FINDINGS*	RESPONSE TO PULSATILE GnRH
1	Infertility	33	Yes	Head trauma, left orchiectomy	—	Partially empty sella	Positive
2	Infertility	27	No	Motor vehicle accident (no head trauma)	—	—	Positive
3	Loss of libido	38	No	—	Marijuana	—	Positive
4	Infertility	29	No	—	Alcohol abuse (until 2 yr before study)	Partially empty sella	Positive
5	Infertility	28	No	—	—	Partially empty sella	Positive
6	Loss of libido	31	No	—	—	Partially empty sella	Positive
7	Impotence	29	Yes	Mumps orchitis, transient limb paralysis	Antihistamines	—	Positive
8	Loss of libido	57	Yes	Depression	Alcohol abuse (until 10 yr before study)	—	None
9	Loss of libido	35	Yes	Depression	Alprazolam, trazodone	—	Not tested
10	Infertility and loss of libido	47	No	—	—	—	Not tested

*Computed tomography or magnetic resonance imaging was performed.

mography or magnetic resonance imaging. Cranial imaging revealed a partially empty sella turcica in the remaining four men (Table 1) and no evidence of an absent or malformed olfactory system, but detailed images of the olfactory region were not done.

Base-line testicular volume in the 10 men (18±5 ml), although smaller than normal, was within the range for normal men and significantly greater than in the men with classic GnRH deficiency (Table 2). All three men who could provide semen specimens were azoospermic. The mean base-line serum luteinizing hormone and follicle-stimulating hormone concentrations in the 10 men were 1.5±1.2 and 2.9±1.7 IU per liter, respectively, values similar to those in men with classic GnRH deficiency and significantly lower than those in normal men (Table 2), and their secretion of luteinizing hormone was not pulsatile (Fig. 1). Their mean serum testosterone concentrations were slightly but significantly higher than in the men with classic GnRH deficiency (78±34 vs. 49±20 ng per deciliter [2.7±1.2 vs. 1.7±0.7 mmol per liter], P=0.004) (Table 2). Their mean serum inhibin B concentrations (an indicator of testicular maturity[12]), although lower than normal, were significantly higher than in the men with classic GnRH deficiency (Table 2). Their serum estradiol concentrations were normal (24±3 pg per milliliter [89±11 pmol per liter]), as were their serum prolactin concentrations (range, 3 to 10 ng per milliliter; normal range, 0 to 15).

One man (Patient 10) had undergone two evaluations of reproductive function before therapy. He was first seen for idiopathic infertility at the age of 43 years, at which time his serum gonadotropin and testosterone concentrations were normal and he had a normal pattern of pulsatile luteinizing hormone

TABLE 2. HORMONE CONCENTRATIONS IN MEN WITH ADULT-ONSET HYPOGONADOTROPIC HYPOGONADISM OR CLASSIC GnRH DEFICIENCY AT BASE LINE AND DURING LONG-TERM ADMINISTRATION OF GnRH.*

GROUP AND PATIENT NO.	BASE LINE						LONG-TERM GnRH THERAPY				
	TESTICULAR VOLUME†	SPERM COUNT	SERUM LH	SERUM FSH	SERUM TESTOSTERONE‡	SERUM INHIBIN B	TESTICULAR VOLUME†	SPERM COUNT	SERUM LH	SERUM FSH	SERUM TESTOSTERONE‡
	ml	×10⁻⁶/ml	IU/liter		ng/dl	pg/ml	ml	×10⁻⁶/ml	IU/liter		ng/dl
Men with adult-onset hypogonadotropic hypogonadism											
1	20	ND	2.9	5.7	34	78	25	83	10.5	29	339
2	20	0.0	0.8	1	45	80	20	4.1	22.1	7.4	371
3	12.5	0.0	0.8	1.9	118	63	23	29	4.1	10.2	564
4	25	ND	0.8	2.2	100	147	25	126	13	5	621
5	20	0.0	1.6	1.8	63	228	25	35	5.9	4.4	449
6	14	ND	0.8	2.1	43	149	NA	NA	NA	NA	NA
7	20	ND	0.8	1.1	57	146	NA	NA	NA	NA	NA
8	23	ND	4.3	4.9	129	124	NA	NA	NA	NA	NA
9	12	ND	0.8	2.9	106	114	NA	NA	NA	NA	NA
10	9	ND	1.8	4.9	84	60	NA	NA	NA	NA	NA
Mean ±SD	18±5	0.0	1.5±1.2	2.9±1.7	78±34	119±52	24±2	55±49	11.1±7.1	11.2±10.2	469±121
P value for the comparison with normal men	0.03		<0.001	<0.001	<0.001	<0.001					
P value for the comparison with men with classic GnRH deficiency	<0.001				0.004	<0.001	<0.001				
Men with classic GnRH deficiency (n=24)	3±2	ND	1.6±1.2	2.4±1.2	49±20	60±21	15±4	34±75	14.0±5.7	10.2±3.8	518±127
P value for the comparison with normal men			<0.001	0.002	<0.001	<0.001	<0.001				
Normal men (n=29)	15–25	25–70	4.7–18.4	1.6–15.7	318–739	87–361	NA	NA	NA	NA	NA

*LH denotes luteinizing hormone, FSH follicle-stimulating hormone, ND not done, and NA not applicable (Patients 6 through 10 received no or only short-term GnRH therapy). Plus–minus values are means ±SD. Values for the normal men are ranges.

†Values are the mean of right and left testicular volumes except in Patient 1, in whom the volume of a single (right) testis is given.

‡To convert values for serum testosterone to nanomoles per liter, multiply by 0.0347.

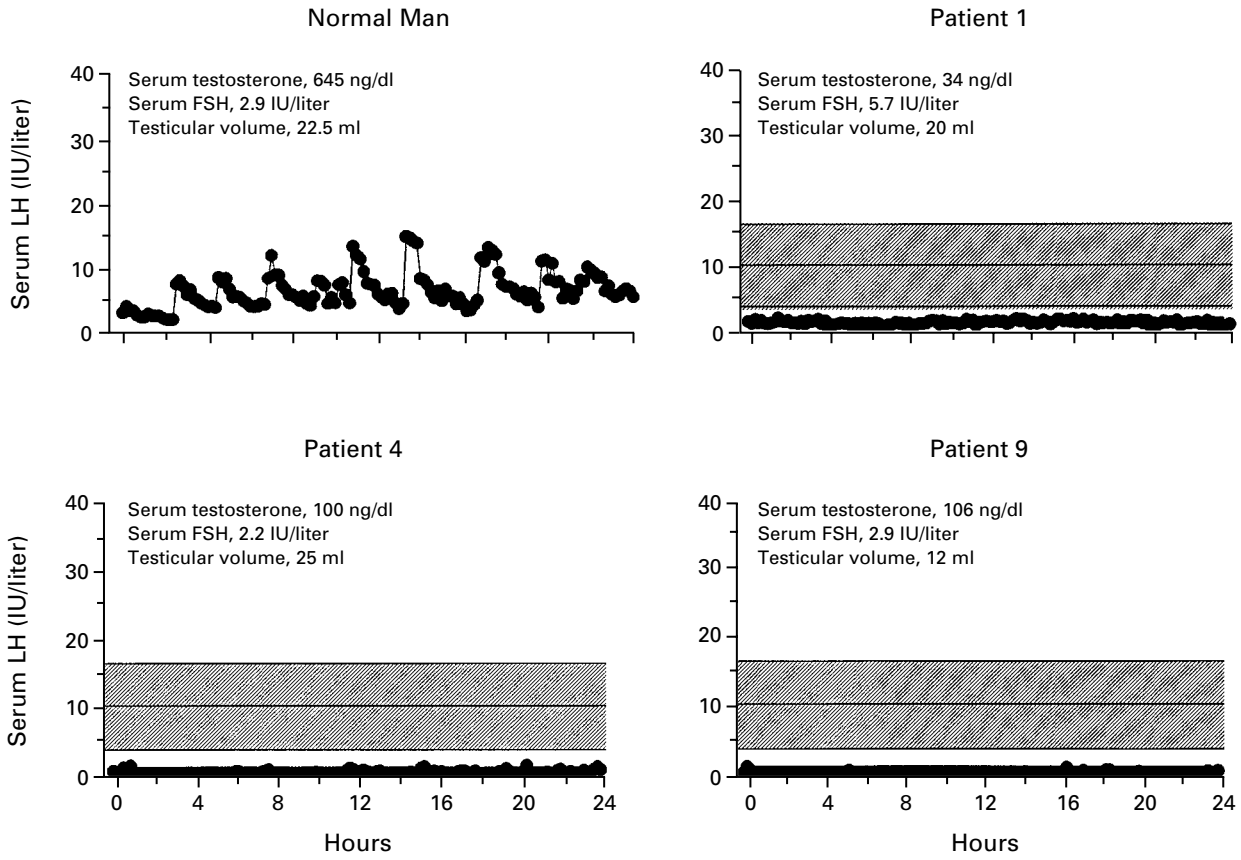

Figure 1. Representative 24-Hour Patterns of Luteinizing Hormone Secretion in a Normal Man and Three Men with Adult-Onset Hypogonadotropic Hypogonadism.

The shaded areas represent the mean (±2 SD) values in 29 normal men. To convert values for serum testosterone to nanomoles per liter, multiply by 0.0347. LH denotes luteinizing hormone, and FSH follicle-stimulating hormone.

secretion (Fig. 2). He returned four years later because of additional symptoms of decreased libido and sexual dysfunction, at which time he had apulsatile luteinizing hormone secretion (Fig. 2).

Response to Pulsatile GnRH Therapy

Seven of the eight men with adult-onset idiopathic hypogonadotropic hypogonadism who received GnRH had normal serum gonadotropin and testosterone concentrations during therapy. One man (Patient 8) had no increase in serum gonadotropin and testosterone concentrations after the administration of GnRH for eight weeks. The five men who received GnRH for at least six months had serum hormonal values similar both to those of similarly treated men with classic GnRH deficiency and to those of normal men (Table 2). Spermatogenesis was restored more rapidly in the five men with acquired hypogonadotropic hypogonadism than in men with classic GnRH deficiency, with maximal sperm concentrations ($55\pm49\times10^6$ per milliliter vs. $34\pm75\times10^6$ per milliliter, $P=0.56$) achieved 33 ± 16 and 92 ± 56 weeks ($P=0.04$), respectively, after the men's serum testosterone concentrations had increased to within the normal range. In all five of these men the results of semen analyses were consistent with fertility, and all three seeking fertility (Patients 1, 2, and 4) fathered a child. The remaining five men chose long-term treatment with either testosterone (Patients 6, 7, 8, and 9) or human chorionic gonadotropin (Patient 10), which restored their libido and sexual function. In Patients 8 and 9, depression did not resolve during testosterone therapy. The men with adult-onset idiopathic hypogonadotropic hypogonadism continued to require treatment for hypogonadal symptoms throughout follow-up (duration, 7 ± 5 years; range, 2 to 16).

DISCUSSION

We have described a group of men with adult-onset idiopathic hypogonadotropic hypogonadism who had no recognizable central nervous system abnormalities. In considering this disorder, several questions should be addressed. First, was the defect

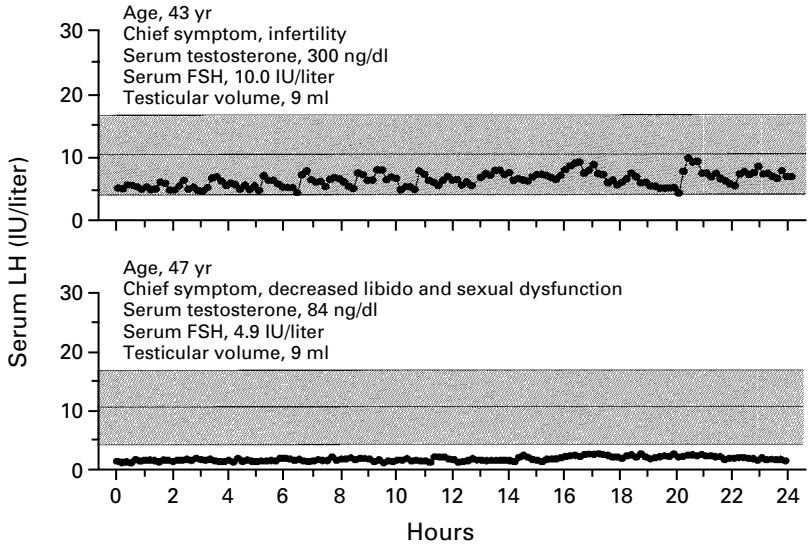

Figure 2. Serial Studies of Luteinizing Hormone Secretion in a Man with Adult-Onset Hypogonadotropic Hypogonadism.

At the time of the second evaluation the patient had symptoms of hypogonadism. The shaded areas represent the mean (±2 SD) values in 29 normal men. To convert values for serum testosterone to nanomoles per liter, multiply by 0.0347. LH denotes luteinizing hormone, and FSH follicle-stimulating hormone.

acquired? Second, were anatomical and functional causes properly excluded? Third, what is the level of the defect?

The normal spontaneous sexual maturation in these men and the documented fertility in several before the onset of their reproductive dysfunction are strong evidence that the defect is acquired. Furthermore, the results of serial studies in one man provide documentation of the development of GnRH deficiency. Thus, both the clinical and biochemical manifestations of adult-onset hypogonadotropic hypogonadism appear to be acquired.

The anatomical causes of acquired hypogonadotropic hypogonadism encompass a large range of disorders, including infiltrative processes and space-occupying lesions such as hemochromatosis,[14] pituitary adenomas and other tumors,[15-17] granulomatous disease,[18-20] and lymphocytic hypophysitis.[21] Hemochromatosis, the disease most likely to cause acquired isolated gonadotropin deficiency in relatively young men, was ruled out by the presence of normal serum ferritin concentrations, and in addition, responsiveness to GnRH is poor in men with hemochromatosis, because of the predominantly pituitary defect in gonadotropin secretion.[22] The importance of the finding of a partially empty sella turcica in 4 of the 10 men is uncertain; about 20 percent of normal subjects have an empty sella without an associated clinical syndrome.[23] One of the men with adult-onset hypogonadotropic hypogonadism had a history of head trauma. However, hypogonadotropic hypogonadism associated with head trauma is usually transient, occurring in the setting of severe traumatic coma associated with concomitant deficiencies of thyroid and adrenal function.[24-26]

In addition to anatomical disorders, psychogenic stress, medical illness, excessive exercise, and malnutrition are known to cause isolated GnRH deficiency in women.[27] It is possible that adult-onset hypogonadotropic hypogonadism as described here is the male counterpart of hypothalamic amenorrhea. Some of these men were depressed or had histories of alcohol or drug abuse, but these disorders are rarely associated with prolonged hypoandrogenemia as severe as in the men we studied.[28] Men with acute medical illness may have substantial transient decreases in serum testosterone and gonadotropin concentrations,[29] but the men we studied were not acutely ill. They were also not exercising excessively or starving themselves, each of which can cause decreased serum testosterone concentrations.[30,31] Thus, neither an anatomical nor a known functional cause of hypogonadism was identified in the men we studied.

Although the severity of other acquired forms of GnRH deficiency (anatomical or functional) varies, the absence of pulsatile luteinizing hormone secretion in these men suggests severe GnRH deficiency. However, their base-line serum testosterone concentrations, although low, were significantly higher than in men with classic GnRH deficiency. This residual Leydig-cell function could reflect minimal residual luteinizing hormone secretion, only detectable with

supersensitive assays,[32] or the post-pubertal nature of their gonadotropin deficiency.

The nearly uniform responsiveness to pulsatile GnRH administration localizes the functional defect in these men to the parvocellular GnRH neuronal system within the hypothalamus. The cause may be defective biosynthesis or secretion of GnRH. Acquired defects of an autoimmune or toxicologic nature resulting in selective destruction of neuromodulators of GnRH secretion within the arcuate-nucleus region of the hypothalamus thus remain a possibility. Autoimmune pituitary disease causing isolated hypogonadotropic hypogonadism is rare in men[21] and would not account for the response of most of our subjects to exogenous GnRH administration. Selective and presumably cell-specific autoimmune destruction of a subgroup of hypothalamic neurons has yet to be described. Finally, it is possible that despite its post-pubertal presentation, adult-onset hypogonadotropic hypogonadism results from the delayed onset of a dominant genetic defect of GnRH secretion, similar to the latent manifestations of familial neurohypophyseal diabetes insipidus, a rare autosomal dominant disorder associated with deficiency of arginine vasopressin.[33] The absence of affected relatives suggests that if there is a genetic cause of this syndrome, the cases described are sporadic.

Although its cause is obscure, adult-onset hypogonadotropic hypogonadism is a unique form of isolated hypogonadotropic hypogonadism arising in sexually mature men. The clinical recognition of this syndrome is important, since it represents one of the few treatable forms of male infertility.

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