

## ORIGINAL ARTICLE

# Reversal of Idiopathic Hypogonadotropic Hypogonadism

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## ABSTRACT

**BACKGROUND**

Idiopathic hypogonadotropic hypogonadism, which may be associated with anosmia (the Kallmann syndrome) or with a normal sense of smell, is a treatable form of male infertility caused by a congenital defect in the secretion or action of gonadotropin-releasing hormone (GnRH). Patients have absent or incomplete sexual maturation by the age of 18. Idiopathic hypogonadotropic hypogonadism was previously thought to require lifelong therapy. We describe 15 men in whom reversal of idiopathic hypogonadotropic hypogonadism was sustained after discontinuation of hormonal therapy.

**METHODS**

We defined the sustained reversal of idiopathic hypogonadotropic hypogonadism as the presence of normal adult testosterone levels after hormonal therapy was discontinued.

**RESULTS**

Ten sustained reversals were identified retrospectively. Five sustained reversals were identified prospectively among 50 men with idiopathic hypogonadotropic hypogonadism after a mean ( $\pm$ SD) duration of treatment interruption of  $6\pm 3$  weeks. Of the 15 men who had a sustained reversal, 4 had anosmia. At initial evaluation, 6 men had absent puberty, 9 had partial puberty, and all had abnormal secretion of GnRH-induced luteinizing hormone. All 15 men had received previous hormonal therapy to induce virilization, fertility, or both. Among those whose hypogonadism was reversed, the mean serum level of endogenous testosterone increased from  $55\pm 29$  ng per deciliter ( $1.9\pm 1.0$  nmol per liter) to  $386\pm 91$  ng per deciliter ( $13.4\pm 3.2$  nmol per liter,  $P<0.001$ ), the luteinizing hormone level increased from  $2.7\pm 2.0$  to  $8.5\pm 4.6$  IU per liter ( $P<0.001$ ), the level of follicle-stimulating hormone increased from  $2.5\pm 1.7$  to  $9.5\pm 12.2$  IU per liter ( $P<0.01$ ), and testicular volume increased from  $8\pm 5$  to  $16\pm 7$  ml ( $P<0.001$ ). Pulsatile luteinizing hormone secretion and spermatogenesis were documented.

**CONCLUSIONS**

Sustained reversal of normosmic idiopathic hypogonadotropic hypogonadism and the Kallmann syndrome was noted after discontinuation of treatment in about 10% of patients with either absent or partial puberty. Therefore, brief discontinuation of hormonal therapy to assess reversibility of hypogonadotropic hypogonadism is reasonable. (ClinicalTrials.gov number, NCT00392756.)

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**C**ONGENITAL IDIOPATHIC HYPOGONADOTROPIC hypogonadism is a disorder characterized by absent or incomplete sexual maturation by the age of 18, in conjunction with low levels of circulating gonadotropins and testosterone and no other abnormalities of the hypothalamo–pituitary axis.<sup>1</sup> Idiopathic hypogonadotropic hypogonadism is caused by an isolated defect in gonadotropin-releasing hormone (GnRH) release, action, or both.<sup>2</sup> Other associated nonreproductive phenotypes, such as anosmia, cleft palate, and sensorineural hearing loss, occur with variable frequency.<sup>3</sup> In the presence of anosmia, idiopathic hypogonadotropic hypogonadism is classified as the Kallmann syndrome, whereas in the presence of a normal sense of smell, it is termed normosmic idiopathic hypogonadotropic hypogonadism. Several genes have been implicated in the pathogenesis of idiopathic hypogonadotropic hypogonadism: *KAL1*,<sup>4,5</sup> *FGFR1*,<sup>6</sup> *GNRHR*,<sup>7,8</sup> *NELF*,<sup>9</sup> and *GPR54*.<sup>10,11</sup>

These genes may act either alone or in combination to cause GnRH deficiency.<sup>12</sup> Exogenous therapy with pulsatile GnRH or gonadotropin therapy usually restores normal pubertal development and fertility, whereas androgen therapy only induces virilization. It is believed that lifelong hormone therapy is required to maintain sexual function and secondary sexual characteristics in men with idiopathic hypogonadotropic hypogonadism.<sup>1</sup> However, rare cases of spontaneous reversal of this condition later in life have been reported.<sup>13–18</sup>

Our clinical experience with patients with idiopathic hypogonadotropic hypogonadism, including the clinical observation of testicular growth in patients receiving androgen therapy, led us to hypothesize that reversal could occur in these patients. We report neuroendocrine and gonadal reversal after discontinuation of hormonal therapy in 15 men with characteristics of idiopathic hypogonadotropic hypogonadism.

**Table 1. Baseline Clinical Characteristics of 15 Men Whose Idiopathic Hypogonadotropic Hypogonadism Was Reversed.\***

Patient No.	Age yr	Diagnosis	Family History†	Associated Phenotypes	Cryptorchidism	Mean Testicular Volume ml
1	18	Kallmann syndrome	nIHH and Kallmann syndrome	None	No	4
2	18	Kallmann syndrome	Delayed puberty, anosmia	Pectus excavatum, color blindness	No	6
3	24	Kallmann syndrome	No	Mild pectus excavatum	No	13
4‡	19	Kallmann syndrome	Delayed puberty	Color blindness, mild hearing loss	No	15
5	20	nIHH	No	None	No	NA
6	18	nIHH	No	Scoliosis, osteoporosis	No	<3§
7	30	nIHH	nIHH	None	Right	2
8	27	nIHH	nIHH	Pectus excavatum, gynecomastia	Right	<4
9	23	nIHH	No	Mild bilateral synkinesia	Right	4
10	20	nIHH	No	None	No	6
11	19	nIHH	No	None	No	8
12	18	nIHH	Delayed puberty	Mild scoliosis	No	12
13	20	nIHH	No	None	No	10
14	20	nIHH	No	None	No	11
15	26	nIHH	No	None	No	17

\* NA denotes not available, and nIHH normosmic idiopathic hypogonadotropic hypogonadism.

† Family history includes GnRH deficiency and olfactory defects.

‡ This patient was treated for growth hormone deficiency from 14 through 18 years of age.

§ The testis was 1 cm in length at the age of 32 years.

## METHODS

## PATIENTS

The criteria for the initial diagnosis of idiopathic hypogonadotropic hypogonadism were an age of at least 18 years, incomplete or absent puberty, a serum testosterone level less than 100 ng per deciliter (3.5 nmol per liter) in the presence of low or normal levels of gonadotropins, otherwise normal pituitary function, and normal hypothalamo-pituitary imaging findings. The patients were studied either at the Massachusetts General Hospital, Boston, or at Newcastle-upon-Tyne University Hospitals, Newcastle, United Kingdom. These studies were approved by the institutional human research committees, and all patients provided written informed consent.

A history of pubertal development and associated nonreproductive phenotypes was obtained, and detailed physical examinations were performed, including measurement of testicular volume with a Prader orchidometer. On the basis of clinical history, testicular size, or both, patients were classified as having either absent or partial puberty.<sup>19</sup> Olfactory acuity was assessed by formal smell testing,<sup>20</sup> and the olfactory system was visualized with magnetic resonance imaging (MRI).<sup>21</sup> In men able to produce an ejaculate, semen analy-

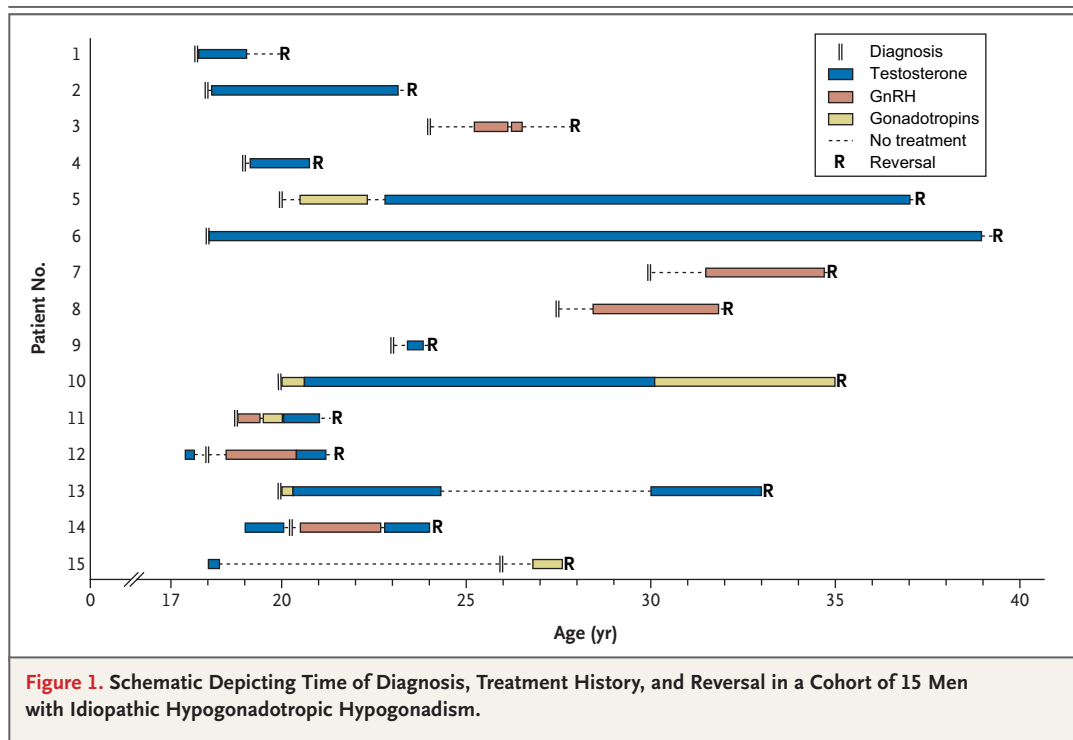
sis was performed according to World Health Organization guidelines.<sup>22</sup>

## IDENTIFICATION OF THE REVERSAL OF IDIOPATHIC HYPOGONADOTROPIC HYPOGONADISM

The criterion for sustained reversal of idiopathic hypogonadotropic hypogonadism was a normal adult endogenous serum testosterone level (at least 270 ng per deciliter [9.4 nmol per liter]) after discontinuation of hormonal therapy. On the basis of the half-life of the drug, the treatment regimen, and the route of administration, the washout periods before assessment were determined as 2 weeks or more for pulsatile GnRH, 4 weeks or more for transdermal testosterone, and 6 to 8 weeks or more for testosterone or human chorionic gonadotropin injections.

Sustained reversal of idiopathic hypogonadotropic hypogonadism was identified either retrospectively or prospectively. Of the 10 men in whom reversal was identified retrospectively, 5 underwent successful initial treatment and had no hypogonadal symptoms after ceasing to adhere to treatment, 3 had reversals after discontinuing hormone therapy for neuroendocrine studies, and 2 had increased testicular size while receiving androgen therapy.

To assess the frequency of sustained reversal of



**Figure 1.** Schematic Depicting Time of Diagnosis, Treatment History, and Reversal in a Cohort of 15 Men with Idiopathic Hypogonadotropic Hypogonadism.

**Table 2. Clinical and Biochemical Characteristics of 15 Men before and after Reversal of Idiopathic Hypogonadotropic Hypogonadism.\***

Patient No.	Age		LH		Testosterone		FSH	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
	yr		IU/liter		ng/dl		IU/liter	
1	18	20	1.6	3.0	58	329	<1.6	1.7
2	18	24	<1.6	11.5	17	344	<1.6	11.7
3	24	28	2.3	6.4	104	401	4.0	7.1
4†	19	21	<1.6	7.8	62	292	2.1	9.7
5†	20	37	<1.6	5.7	47	325	<1.6	2.3
6†	18	39	3.2	4.6	20	350	2.1	2.7
7	30	35	<1.6	11.1	66	514	<1.6	17.0
8	27	32	<1.6	20.2	35	505	4.5	50.5
9†	23	24	6.5	9.8	73	391	6.7	12.8
10	20	35	3.5	5.5	29	317	2.7	2.3
11	19	21	2.3	9.8	24	595	2.4	7.4
12	18	23	4.5	8.6	103	440	3.2	5.8
13	20	33	1.6	2.4	32	346	<1.6	1.9
14†	20	23	6.8	14.6	85	374	2.7	6.3
15	26	27	3.6	7.1	71	271	2.4	3.9
All 15 patients with reversals	21±4	28±6	2.7±2.0	8.5±4.6	55±29	386±91	2.5±1.7	9.5±12.2
50 Healthy men		24±6		10±2.8		533±135		5.7±2.1
45 Patients without reversals	25±7	32±8	1.5±1.5	1.6±1.5	37±24	24±23	1.5±1.4	1.9±2.3

\* Plus-minus values are means ±SD. LH denotes luteinizing hormone, FSH follicle-stimulating hormone, and NA not available.

† Spermatogenesis was revealed by a testicular biopsy.

idiopathic hypogonadotropic hypogonadism, we conducted a 3-year prospective study that identified five men with reversal. The patients were identified from January 2003 through April 2006. Fifty men who had previously received a diagnosis of idiopathic hypogonadotropic hypogonadism agreed to come to the Reproductive Endocrine Unit of the Massachusetts General Hospital for a physical examination, biochemical profiling, neuroendocrine evaluation, and semen analysis after discontinuation of hormone-replacement therapy.

#### BIOCHEMICAL PROFILE

The patients discontinued hormone therapy before undergoing biochemical measurements. Serum testosterone levels were measured on two separate occasions, and the serum levels of luteinizing hormone, follicle-stimulating hormone, testosterone, inhibin B, and sex hormone-binding globulin (SHBG) were measured as previously de-

scribed.<sup>19,23</sup> For patients who underwent neuroendocrine evaluation, these biochemical tests were performed on a serum pool from a 12-hour sampling.

#### NEUROENDOCRINE EVALUATION

For patients who underwent neuroendocrine evaluation, an overnight frequent blood-sampling study (every 10 minutes for 12 hours) was performed at the Massachusetts General Hospital to determine the endogenous secretion pattern of luteinizing hormone. Pulsatile luteinizing hormone secretion was analyzed with the use of a validated modified version of the Santen and Bardin method.<sup>24,25</sup>

#### PEDIGREE ANALYSIS AND GENETIC STUDIES

The family history was obtained for each patient. Exons and exon-intron boundaries were amplified by standard polymerase-chain-reaction techniques for GNRHR (GenBank accession number

Inhibin B		Mean Testicular Volume		Sperm Count		Time after Reversal yr	Postreversal Follow-up	
Baseline pg/ml	Follow-up	Baseline ml	Follow-up	Baseline $\times 10^{-6}/ml$	Follow-up		No. of Blood Samples	Mean Serum Testosterone ng/dl
NA	NA	4	25	NA	NA	8	1	360
NA	99	7	9.5	No ejaculate	2	5.1	4	310
89	NA	13	17.5	No ejaculate†	65	23.7	3	309
NA	268	15	12	No ejaculate	97	3.9	4	350
NA	79	NA	5.5	NA	30	1.6	7	412
NA	91	<3	13	0	13	2	7	337
50	126	2	10	0	Present‡	0.8	5	441
103	92	3.5	11	No ejaculate	NA	20.8	4	574
136	58	4	7.5	NA	0.3	1.8	7	321
NA	NA	6	25	NA	51	0.8	2	288
NA	178	8	25	No ejaculate	2	20.7	4	470
164	172	12	20	No ejaculate	Present‡	2.5	5	361
NA	NA	10	25	NA	152	5.0	4	411
203	197	11	14	NA	0.1	1.9	6	368
63	233	17	20	No ejaculate	146	0.6	3	216
115±55	145±69	8±5	16±7	None measured	51±58	6.5±8.4	5±2	369
	175±50		23±3		111±76			
NA	63±58	4±3	7±5					

AH005567),<sup>7</sup> *KAL1* (M97252),<sup>26</sup> *GPR54* (AY253981),<sup>11</sup> and *FGFR1* (BC018128).<sup>17</sup> Frameshift insertions or deletions and nonsense changes were categorized as mutations. Other nucleotide changes were considered mutations when they were absent from the National Center for Biotechnology Information (NCBI) database of single-nucleotide polymorphisms (dbSNP) and the expressed sequence tags database and absent in at least 170 ethnically matched healthy controls.

#### STATISTICAL ANALYSIS

Summary data are expressed as means  $\pm$ SD. Within-group comparisons were performed by paired t-tests, except for comparisons of follicle-stimulating hormone levels, for which the Wilcoxon signed-rank test was used because of one extremely high value among the results. In these analyses, undetectably low gonadotropin levels were assigned a value of 0.8 IU per liter, the midpoint between zero and the assay level of detection. All tests were

two-sided, and a P value less than 0.01 was considered to indicate statistical significance.

## RESULTS

#### CLINICAL AND BIOCHEMICAL CHARACTERISTICS

Five patients with idiopathic hypogonadotropic hypogonadism meeting the criterion for reversal were identified prospectively, and 10 were identified retrospectively. The clinical characteristics of the 15 men with sustained reversal are summarized in Table 1. The mean age at diagnosis was 21 years (range, 18 to 30). Eleven of the men (73%) had normosmic idiopathic hypogonadotropic hypogonadism, and four (27%) had the Kallmann syndrome. Two of the latter men (Patients 2 and 4) had no olfactory bulbs on MRI. Nine patients had some degree of spontaneous pubertal development, and puberty was absent (testicular volume, 4 ml or less) in the other six.

Figure 1 shows a timeline of hormonal treat-

ment for each patient from diagnosis to the documentation of reversal. After diagnosis, all patients with idiopathic hypogonadotropic hypogonadism received hormonal treatment for a period ranging from 5 months to 21 years; five men were treated with testosterone alone, three men received pulsatile GnRH therapy only, and seven men received a mixed regimen that could include testosterone, gonadotropins, or GnRH. Regardless of the specific regimen, all patients were exposed to androgens while receiving therapy.

Table 2 shows the clinical and biochemical evidence of reversal for each patient. These data are contrasted with results from the time of diagnosis of idiopathic hypogonadotropic hypogonadism. There were significant increases in the levels of serum luteinizing hormone, from  $2.7 \pm 2.0$  to  $8.5 \pm 4.6$  IU per liter ( $P < 0.001$ ); follicle-stimulating hormone, from  $2.5 \pm 1.7$  to  $9.5 \pm 12.2$  IU per liter ( $P < 0.01$ ); and testosterone, from  $55 \pm 29$  ng per deciliter ( $1.9 \pm 1.0$  nmol per liter) to  $386 \pm 91$  ng per deciliter ( $13.4 \pm 3.2$  nmol per liter,  $P < 0.001$ ). Post-reversal adult testosterone levels occurred with normal levels of serum SHBG ( $29.3 \pm 10$  nmol per liter; reference range, 11 to 71 nmol per liter). Testicular volume increased from  $8 \pm 5$  ml to  $16 \pm 7$  ml ( $P < 0.001$ ), and 12 men had normal testicular volume (12 ml or more). Four men (Patients 1, 2, 6, and 9) had had previous testicular growth while receiving testosterone-replacement therapy only. Thirteen men who provided semen samples had sperm in their ejaculate. Serum inhibin B levels remained relatively low in Patients 2, 5, 6, 8, and 9, a result consistent with their lower testicular volumes and lower sperm counts.

#### NEUROENDOCRINE STUDIES

Seven men with idiopathic hypogonadotropic hypogonadism underwent repeated detailed neuroendocrine studies. At diagnosis, the mean serum luteinizing hormone level was  $3.9 \pm 1.9$  IU per liter, and six men had either no luteinizing hormone pulses or decreased luteinizing hormone frequency in the setting of hypogonadal testosterone (Fig. 2). One patient (Patient 14) displayed normal luteinizing hormone secretion. However, in the presence of hypogonadal serum testosterone, he met the diagnostic criteria for idiopathic hypogonadotropic hypogonadism. After reversal, we documented normal mean luteinizing hormone levels ( $10.2 \pm 4.2$  IU per liter), luteinizing hormone pulse frequencies

#### Figure 2 (facing page). Neuroendocrine Profile and Serum Testosterone before and after Reversal of Idiopathic Hypogonadotropic Hypogonadism.

Overnight sampling studies (every 10 minutes for 12 hours) depicting endogenous luteinizing hormone (LH) secretion are shown. Inverted triangles denote LH pulses. The shaded regions show the normal range of serum LH in men. To convert testosterone (T) values to nanomoles per liter, multiply by 0.03467.

( $8 \pm 3$  pulses per 12 hours), and luteinizing hormone pulse amplitudes ( $4.8 \pm 2.2$  IU per liter) in all patients.

#### PEDIGREE ANALYSIS

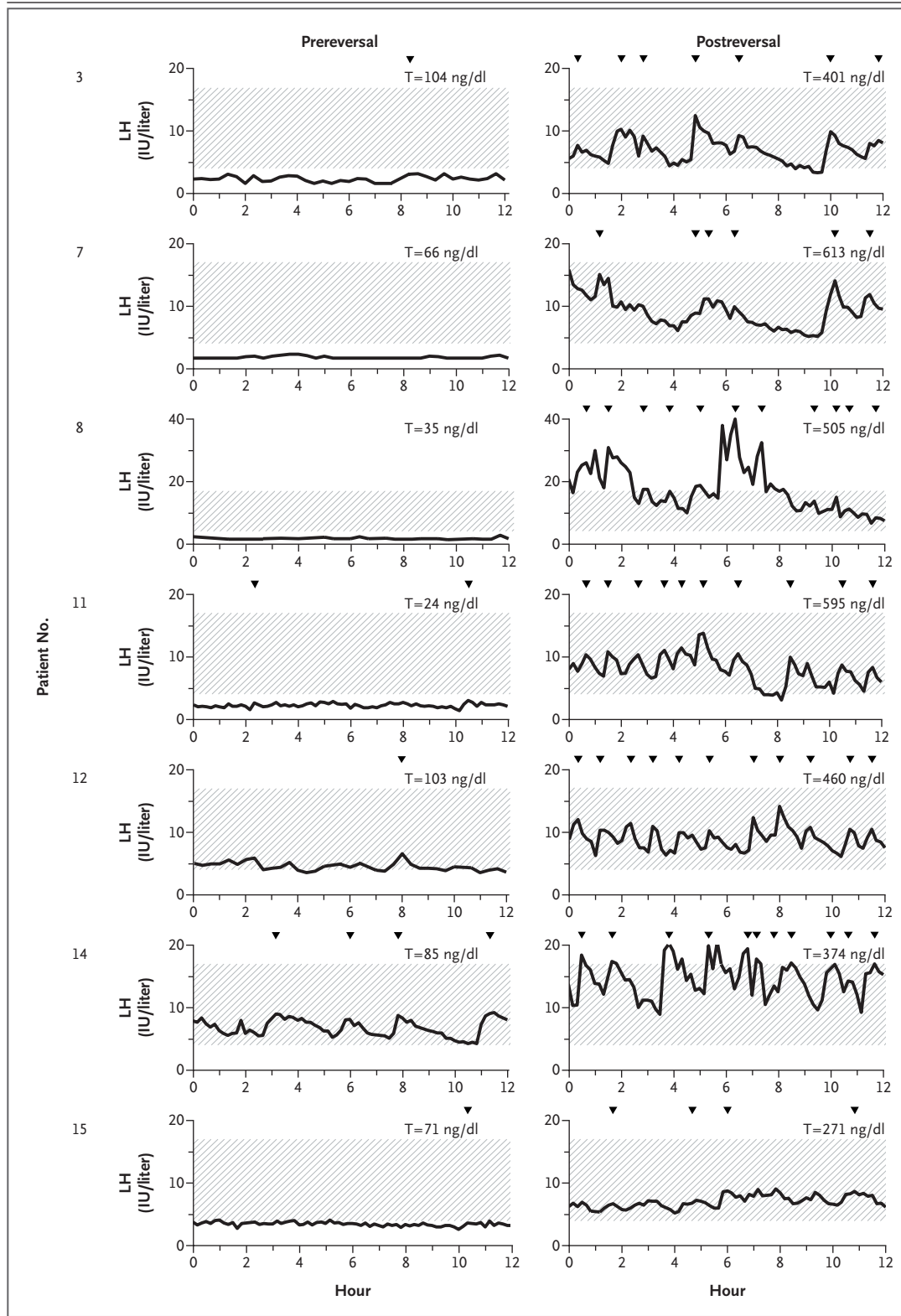
Idiopathic hypogonadotropic hypogonadism was sporadic in nine men and familial in six (Table 1). One family included four members with normosmic idiopathic hypogonadotropic hypogonadism (Fig. 3A). Three of these subjects underwent long-term GnRH therapy with adequate responses in terms of serum testosterone and testicular growth. Two siblings (II-1 and II-2; Patients 8 and 7, respectively) displayed reversal after discontinuing GnRH pulse therapy, whereas the third brother (II-10) remained hypogonadal (Fig. 3B).

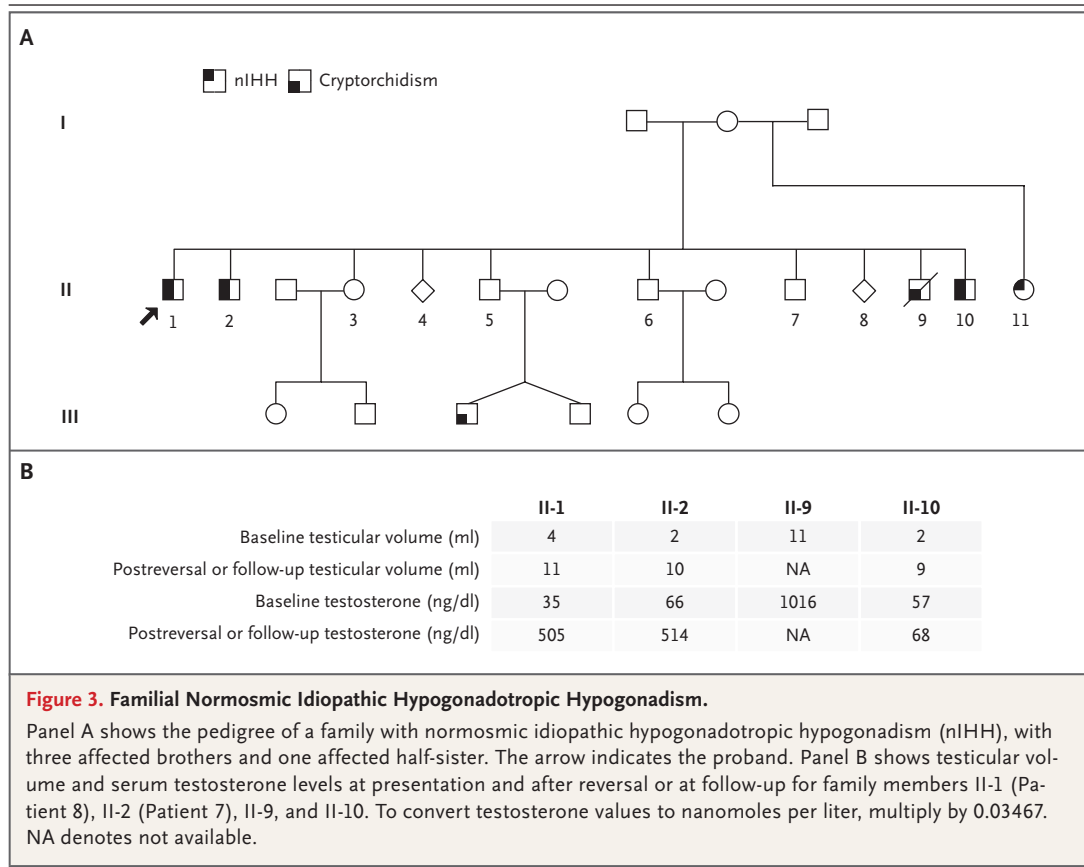
#### GENETIC SCREENING

Mutations in *FGFR1* or *GNRHR* were identified in 3 men (of 13 who were screened) who had reversal of idiopathic hypogonadotropic hypogonadism. The patients with a homozygous *GNRHR* mutation (c.317 G→A, p.Gln106Arg [Patient 15 in Table 1]) and a heterozygous *FGFR1* mutation (c.1864 C→T, p.Arg622X [Patient 2 in Table 1]) have been previously reported.<sup>16,17</sup> In addition, Patient 14 (Table 1) harbors an *FGFR1* mutation (c.296 A→G) leading to an amino acid substitution p.Tyr99Cys, a mutation previously described in a patient with the Kallmann syndrome.<sup>6</sup>

#### THREE-YEAR PROSPECTIVE STUDY

Five of 50 men with idiopathic hypogonadotropic hypogonadism (Patients 4, 5, 6, 9, and 14) met the criterion for reversal of hypogonadism — that is, a serum testosterone level characteristic of adult men; their average testosterone level was  $346 \pm 39$  ng per deciliter ( $12.0 \pm 1.4$  nmol per liter) (Table 2 and Fig. 4). The rate of reversal was 10% (95% confidence interval, 2 to 18). Patients with reversal were identified at a mean of  $6 \pm 3$  weeks after dis-





continuation of hormonal therapy. The rate of reversal was similar among men with absent puberty (testicular volume,  $\leq 4$  ml) and among those with partial puberty (testicular volume,  $>4$  ml): 2 of 18 (11%) and 3 of 32 (9%), respectively. The remaining 45 men with idiopathic hypogonadotropic hypogonadism remained hypogonadotropic and hypogonadal after discontinuing therapy for  $7 \pm 4$  weeks (Table 2 and Fig. 4).

#### POSTREVERSAL FOLLOW-UP

We followed the patients for an average of 6.5 years (range, 0.6 to 23.7) after reversal (Table 2). Thirteen patients had normal adult serum testosterone levels through the entire follow-up period. Patient 2 had normal serum testosterone levels for 2 years but then became hypogonadal, with a serum testosterone level of 116 ng per deciliter (4.0 nmol per liter), after the development of severe depression. Patient 15 had relatively low endogenous testosterone levels (Table 2) and continued to have increased sperm counts after the last serum testos-

terone measurement but subsequently was lost to follow-up.

#### DISCUSSION

Episodic secretion of GnRH from the hypothalamus is a key requirement for the initiation and maintenance of a normal reproductive axis in humans. However, the genetic and environmental factors modulating the secretion of this hormone remain poorly understood.

Our results indicate that reversal of hypogonadotropic hypogonadism occurs across a broad spectrum of GnRH deficiency and its related phenotypes. Consistent with the few case reports published to date, the present cohort of men with sustained reversal of idiopathic hypogonadotropic hypogonadism includes patients with the Kallmann syndrome and patients with normosmic idiopathic hypogonadotropic hypogonadism.<sup>13-18</sup> It is notable that reversal occurred in Patient 3, who had a "fertile eunuch" variant of idiopathic hypo-

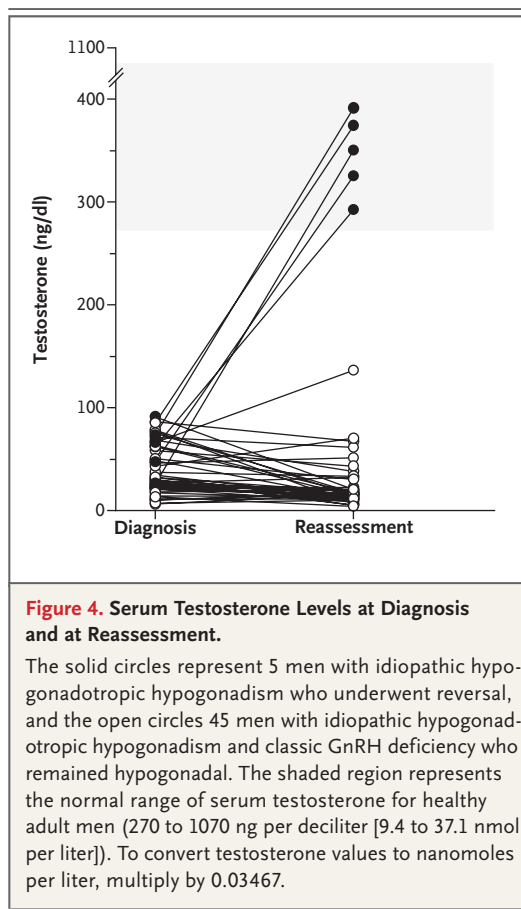


gonadotropic hypogonadism characterized by lack of virilization and hypogonadal serum testosterone levels but active spermatogenesis.<sup>27</sup> Furthermore, reversals occurred both in men with absent puberty and in men with partial puberty, suggesting that evidence of previous endogenous GnRH secretion is not predictive of future reversal of idiopathic hypogonadotropic hypogonadism. However, testicular growth, a biomarker of gonadotropin secretion over time, represents a subtle yet key factor pointing to reversal of idiopathic hypogonadotropic hypogonadism, as evidenced by testicular growth during androgen therapy in four patients with reversal of idiopathic hypogonadotropic hypogonadism.

All patients who underwent reversal had testosterone levels similar to those in a cohort of healthy adult men (Table 2). Furthermore, the postreversal neuroendocrine profiles demonstrated activation of the hypothalamo–pituitary–gonadal axis in adulthood. After reversal, spermatogenesis occurred in all patients assessed. The suboptimal sperm counts seen in a few patients probably reflect previous abnormal activation of the hypothalamo–pituitary–gonadal axis during early infancy, a period critical for stimulation of proliferation of Sertoli cells and future sperm-producing capacity by GnRH-induced gonadotropin.<sup>28,29</sup> However, men with idiopathic hypogonadotropic hypogonadism and oligospermia have demonstrated fertility even with sperm counts below 1 million per milliliter.<sup>30</sup>

In this study, 10% of the 50 men with idiopathic hypogonadotropic hypogonadism who discontinued reproductive hormonal therapy maintained adult levels of serum testosterone, revealing a relatively high incidence of reversal. There are practical implications of this observation. We would suggest that patients with idiopathic hypogonadotropic hypogonadism, with or without anosmia and regardless of their previous pubertal development, should be informed of the possibility of fertility and the spontaneous reversal of hypogonadism. In addition, men with idiopathic hypogonadotropic hypogonadism should be reassessed for recovery of the hypothalamo–pituitary–gonadal axis.

In contrast to patients with constitutional delay of puberty, all patients in the present study received a diagnosis of idiopathic hypogonadotropic hypogonadism at or after the age of 18. Moreover, seven patients presented with characteristics not



typically seen in constitutional delay of puberty, such as unilateral cryptorchidism, anosmia, and synkinesia. However, we have previously demonstrated that the rate of delayed puberty in families with idiopathic hypogonadotropic hypogonadism is 12 times as high as normal,<sup>31</sup> and some patients with delayed puberty carry the same gene defects as the probands with idiopathic hypogonadotropic hypogonadism.<sup>17,32</sup> Therefore, it is possible that this reversible variant form of idiopathic hypogonadotropic hypogonadism and delayed puberty both lie on the milder end of the phenotypic spectrum of GnRH deficiency.

The number of neurons producing GnRH in the human hypothalamus is relatively small (<2000), and these neurons are distributed as a diffuse network, rather than as a discrete nucleus.<sup>33</sup> Such anatomy may render the GnRH pulse generator functionally vulnerable to minor perturbations, leading to GnRH deficiency and hypogonadotropic hypogonadism.

In the present study, we identified two *FGFR1*

mutations, one associated with the Kallmann syndrome in a patient with reversal<sup>17</sup> and another associated with normosmic idiopathic hypogonadotropic hypogonadism in another patient with reversal. Although defects in *FGFR1* signaling are thought to cause the Kallmann syndrome by disrupting development of the olfactory bulb,<sup>6,34</sup> the patient with normosmic idiopathic hypogonadotropic hypogonadism who underwent reversal apparently had a normal olfactory system. Consistent with this phenotype, a murine model with dominant negative *FGFR1* targeted to GnRH-producing neurons has normal olfactory bulbs but a 30% decrease in the population of GnRH-producing neurons in the hypothalamus, resulting in delayed puberty.<sup>35</sup> Therefore, these two cases of sustained reversal in patients with an *FGFR1* mutation indicate that a genetic defect leading to idiopathic hypogonadotropic hypogonadism can be overcome, probably by an environmental stimulus such as exposure to sex steroids. Alternatively, a genetic defect may considerably lengthen the time required to achieve a mature network of GnRH-producing neurons that is capable of delivering synchronized endogenous GnRH pulses, rather than completely interdicting their development, as previously thought.

Although the precise mechanism of reversal of hypogonadotropic hypogonadism is unclear, the mechanism may involve plasticity of the GnRH-producing neurons in adulthood. Plasticity, defined as the ability of the nervous system to adapt

in response to the environment, is a striking feature of the vertebrate brain. For example, the size and function of the nuclei that regulate singing behavior in songbirds are modulated by environmental cues and sex steroids.<sup>36</sup>

Although neurogenesis in humans is thought to occur primarily during embryonic and early postnatal stages, multipotential progenitor cells residing in the subcortical white matter of the adult human brain have recently been identified as having the potential to replace neuronal lineages.<sup>37</sup> Furthermore, neurons in the olfactory epithelium, the olfactory bulbs, and the dentate gyrus of the hippocampus are generated throughout life,<sup>38-40</sup> and their generation appears to be modulated by sex steroids.<sup>41</sup> Indeed, exposure to sex steroids, although the length of exposure was variable, seems to be a common denominator in our patients who underwent reversal. We therefore speculate that sex steroids enhance the plasticity of the neuronal network producing GnRH in the adult human brain, leading to reversal of hypogonadotropic hypogonadism.

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