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- Recognize the symptoms and signs of hypogonadism throughout different phases of life.
- Identify the congenital and acquired causes of hypogonadotropic hypogonadism.
- Diagnose hypogonadotropic hypogonadism.

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Approach to the Patient With Hypogonadotropic Hypogonadism

Letícia Ferreira Gontijo Silveira and Ana Claudia Latronico

Unidade de Endocrinologia do Desenvolvimento, Laboratório de Hormônios e Genética Molecular/LIM42, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, 05403-000 Brazil

Hypogonadotropic hypogonadism (HH) or secondary hypogonadism is defined as a clinical syndrome that results from gonadal failure due to abnormal pituitary gonadotropin levels. HH may result from either absent or inadequate hypothalamic GnRH secretion or failure of pituitary gonadotropin secretion. Several congenital and acquired causes, including functional and organic forms, have been associated with this condition. One important aspect of the HH diagnosis is that it may reflect the presence of a tumor of the hypothalamic pituitary region or even a systemic disease. On the other hand, functional forms of HH, characterized by a transient defect in GnRH secretion, are relatively common in women, in response to significant weight loss, exercise, or stress leading to hypothalamic amenorrhea. HH is typically characterized by low circulating sexual steroids associated with low or inappropriately normal gonadotropin levels. The precise and early diagnosis of HH can prevent negative physical and psychological sequelae, preserve normal peak bone mass, and restore the fertility in affected patients. **(*J Clin Endocrinol Metab* 98: 1781–1788, 2013)**

Case Report

A 19 year-old female, born from nonconsanguineous parents, was referred to the Endocrinology Unit due to primary amenorrhea and poor breast development. Spontaneous partial pubarche and thelarche occurred at 13 and 15 years, respectively. The patient did not report eating disorders or vigorous physical activity. She had no olfactory complaints. She had 2 older brothers with a history of normal pubertal development. At physical examination, she had eunuchoid habitus (height, 155 cm; arm span, 160 cm), weight of 60.7 kg, with normal body mass index of 23 kg/m^2. Pubic hair and breast development were Tanner stage II. She had ogival palate and cavus feet, and no other stigmata were observed. Basal hormonal evaluation revealed low serum estradiol (6.8 pg/ml) and suppressed LH (<0.6 IU/L) and FSH (<1.0 IU/L) levels. Upon acute GnRH stimulation

Abbreviations: hCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; IHH, isolated HH; MRI, magnetic resonance imaging.

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Table 1. Genes and Their Protein Products Associated With Congenital IHH Phenotype

Genes	Locus	Gene Product	Function	Inheritance	Phenotype
KAL-1	Xp22.3	Anosmin-1	Migration of GnRH neurons	X-linked	Kallmann syndrome
FGF8 *FGFR1*	10q25 8p11.2	Fibroblast growth factor receptor 8 and its receptor 1	Migration of GnRH neurons	Autosomal dominant	Kallmann syndrome or normosmic IHH
NELF	9q34.3	Nasal embryonic LHRH factor	Migration of GnRH neurons	Autosomal dominant?	Kallmann syndrome
PROK2 *PROKR2*	3p13 20p12.3	Prokineticin-2 and its receptor	Migration of GnRH neurons	Autosomal dominant and recessive	Kallmann syndrome or normosmic IHH
GNRH1 *GNRH-R*	8p21-11.2 4q13.2-3	GnRH and its receptor	Stimulation of gonadotropins and GnRH signaling	Autosomal recessive	Normosmic IHH
KISS1 KISS1R	1q32 19p13.3	Kisspeptin and its receptor	Stimulation of GnRH secretion	Autosomal recessive	Normosmic IHH
DAX1 or NROB1	X21.3-21.2	Orphan nuclear receptor	Regulation of pituitary and hypothalamic gene transcription	X-linked	Adrenal insufficiency and normosmic IHH
LEP *LEPR*	7q31.3 1p31	Leptin and its receptor	Modulator of GnRH secretion	Autosomal recessive	Severe obesity and normosmic IHH
TAC3 *TACR3*	12q13-12 4q25	Neurokinin B and its receptor	Stimulation and inhibition of GnRH secretion	Autosomal recessive	Normosmic IHH
WDR11	10q	WD protein	Development of olfactory neurons	Autosomal dominant	Kallmann syndrome or normosmic IHH
CHD7	8q12.1-q12.2	Chromodomain helicase DNA-binding protein	Positive regulator of ribosomal RNA biogenesis	Autosomal dominant	Kallmann syndrome or normosmic IHH
SEMA3A	7p12.1	Semaphorin-3A	Axonal path finding of GnRH neurons	Autosomal dominant	Kallmann syndrome
HS6ST1	Xq26.2	Heparan sulfate 6-O-sulfotransferase 1	Heparan sulfate modifier	Complex trait	Kallmann syndrome or normosmic IHH

test (100 mg iv), peak LH was 1.4 IU/L and peak FSH was 1.7 IU/L. Anterior pituitary function was otherwise normal, including prolactin (9 ng/mL) and thyroid function (TSH, 1.5 μIU/L; free T_4, 1.1 ng/dL). A formal olfactory test was applied and confirmed normal sense of smell. Her bone age was 13 years. No abnormalities were noticed on abdominal ultrasound examination. Pelvic ultrasound revealed infantile uterus (1.5 cc) and small ovaries (right, 2.6 cc; left, 1.3 cc). Her bone mineral density, corrected for bone age, was reduced, showing osteopenia. Magnetic resonance imaging scan of the hypothalamic-pituitary region was normal.

Table 2. Acquired Causes of HH

Tumors: prolactinomas, Rathke's pouch cysts, craniopharyngiomas, germinomas, teratomas, meningiomas, gliomas, astrocytomas, metastatic tumors (breast, lung, prostate)
Functional gonadotropin deficiency: chronic systemic disease, acute illness, malnutrition, primary hypothyroidism, hyperprolactinemia, obesity, diabetes mellitus, Cushing's syndrome, anorexia nervosa, bulimia, auto immune disease, nephrotic syndrome, sickle cell disease, thalassemia, alcoholism
Infiltrative diseases: hemochromatosis, sarcoidosis, granulomatous diseases, histiocytosis X, lymphocytic hypophysitis
Infections: tuberculosis, HIV/AIDS, syphilis, fungus
Trauma: contusion, skull fracture, pituitary stalk transaction, hypophysectomy
Vascular: ischemia, Sheehan's syndrome, pituitary apoplexy
Drugs: opioids, anabolic steroids, corticoids, narcotics

Background

Pulsatile secretion of GnRH by hypothalamic neurons is a crucial element of the reproductive cascade, initiating the release of pituitary gonadotropins, gonadal secretion of sex steroids, pubertal development, and gametogenesis. Hypogonadotropic hypogonadism (HH) is characterized by failure of gonadal function secondary to deficient gonadotropin secretion (1). This condition is commonly seen in association with other pituitary hormone deficiency states caused by structural lesions of the hypothalamic-pituitary region. However, congenital, acquired, and functional causes have been associated with isolated GnRH deficiency (Tables 1 and 2) (2).

Congenital Causes

Congenital isolated HH (IHH) is characterized by partial or complete lack of pubertal development, secondary to deficient GnRH-induced gonadotropin secretion, in the absence of anatomical abnormalities in the hypothalamic and pituitary region, and normal baseline and reserve testing of the remaining pituitary hormones (1). This genetic condition is classically divided in 2 groups based on the presence or absence of olfaction dysfunction. Around 50–60% of the affected individuals exhibit anosmia or hyposmia in association with IHH, defining Kallmann syndrome. Patients with Kallmann syndrome may have additional phenotypic abnormalities including craniofacial defects (cleft lip/palate, high-arched palate, ocular hypertelorism, dental agenesis), neurosensory deafness, digital anomalies (clinodactyly, syndactyly, camptodactyly), unilateral renal agenesis, and neurological defects (oculomotor abnormalities, bimanual synkinesis or mirror hand movements, cerebellar ataxia), whereas normosmic IHH is usually not associated with any other malformations (nonsyndromic condition) (3). In Kallmann syndrome, anosmia is related to hypoplasia or aplasia of the olfactory bulbs, whereas the hypogonadism is due to GnRH deficiency, due to defective migration of olfactory and GnRH neurons. In most vertebrates, the olfactory and GnRH neurons share a common origin in the nasal placode and migrate together across the cribiform plate toward the developing olfactory bulb, explaining the association of HH with olfactory abnormalities (4, 5).

Congenital IHH is a clinically and genetically heterogeneous disorder. Although sporadic cases are the most frequent, families with congenital IHH have been reported with X-linked, autosomal dominant or recessive inheritance. The prevalence of IHH has been estimated at 1/4000 to 1/10 000 males, and it is reported to be 2 to 5 times less frequent in females. The reason for this marked gender discrepancy is not known, and the prevalence of the disease is probably underestimated in females. Male preponderance can be only partially explained by the contribution of men with X-linked disease to the total number of cases (1, 6, 7). Other factors, such as incomplete penetrance, biased referral patterns, with male patients being seen by endocrinologists as opposed to more females being referred and treated by gynecologists, should also be considered.

A growing list of genes has been implicated in the molecular pathogenesis of the congenital IHH, pointing up the heterogeneity and complexity of the genetic basis of this condition (Table 2). These genes encode neuropeptides and proteins involved in the development and migration of GnRH neurons, or in the control of different stages of GnRH function. Mutations in *KAL1*, *FGFR1/FGF8*, *PROK2/PROKR2*, *NELF*, *CHD7*, *HS6ST1*, *WDR11*, and *SEMA3A* are associated with defects in neuronal migration, leading to Kallmann syndrome (8–10). Notably, defects in *FGFR1*, *FGF8*, *PROKR2*, *CHD7*, and *WDR11* have also been associated with normosmic IHH, although in a lower frequency (8, 10). Mutations in *KISS1/KISS1R*, *TAC3/TACR3*, and *GNRH1/GNRHR*, genes that interfere in the secretion and action of GnRH, are described exclusively in patients with normosmic IHH (8, 11). Despite these recent and great advances, the genetic basis of most cases of congenital IHH remains unknown, with the molecular basis of this condition being identified in approximately 30% of patients.

Congenital IHH has been historically defined in traditional Mendelian terms and considered a monogenic disease. However, this concept has been recently reviewed. Pedigrees with great phenotypic variability have been described, and complex genetic transmission (digenic or oligogenic inheritance) has been recently demonstrated (12, 13). Substantial variation in clinical expression of the same genetic defect in families of patients with IHH has been observed, with affected members presenting with Kallmann syndrome, normosmic IHH, isolated anosmia, isolated clefting, simple pubertal delay, or even apparent phenotypic normality, suggesting the possibility that Kallmann syndrome and normosmic IHH may take part of a wider spectrum of disease (3, 10, 13). This variability has been observed mainly in kindreds with mutations in *FGF8/FGFR1* and in *PROK2/PROKR2* ligand-receptor pairs (3, 13). This type of phenotypic heterogeneity may be ascribed to environmental or epigenetic effects. A second explanation is the coexistence within families of defects in 2 or more different genes that interact functionally, as it has recently been described in a number of families (10, 13).

Acquired and Functional Causes

Acquired causes of HH are mostly due to structural or functional abnormalities involving the hypothalamic-pituitary axis, and most of these patients have multiple pituitary hormone deficiencies. These conditions include infiltrative disorders of the hypothalamic-pituitary tract, such as sarcoidosis, lymphocytic hypophysitis and histiocytosis, space-occupying lesions such as pituitary adenomas, craniopharyngiomas, and other central nervous system tumors (2).

Adult-onset isolated gonadotropin deficiency can be secondary to systemic disorders, drugs, functional abnormalities, or idiopathic. One of the most frequent causes of

acquired isolated HH is hyperprolactinemia. Elevated prolactin levels can result mainly from the use of drugs that interfere with the dopaminergic system, lactotroph adenomas (prolactinomas), or from any hypothalamic or pituitary stalk disorder that interrupts hypothalamic inhibition of prolactin secretion. The possibility of nutritional disorders or an undiagnosed chronic illness that may affect the hypothalamic GnRH pulse generator should be evaluated in patients with HH. Hypothyroidism should be ruled out, particularly if growth velocity is below expected and bone age markedly delayed. Hemochromatosis can affect the hypothalamic and pituitary region, leading to progressive isolated gonadotropin deficiency, and should always be ruled out by the presence of normal serum ferritin concentrations. Drugs that can reversibly suppress sex steroid levels include opiates, glucocorticoid, and psychotropic agents such as phenothiazines.

The idiopathic form of adult-onset HH is a rare disorder characterized by an isolated failure of gonadotropin secretion occurring after an otherwise normal sexual maturation in men in whom anatomical, systemic, or functional causes had been ruled out (14). No genetic defect in genes associated with congenital IHH has been identified in this group of patients (15). Long-term follow-up of adult-onset HH individuals revealed that the clinical and hormonal characteristics of these patients did not change over a decade, all of them remaining severely hypogonadal, with testosterone levels below 130 ng/dL, with no spontaneous reversals (15). It is important to differentiate adult-onset HH, characterized by frankly low serum testosterone levels in the presence of low or normal gonadotropins, from the progressive testosterone deficiency observed in a small minority of aging men, known as late-onset hypogonadism. This latter condition has been defined as a syndrome in middle-aged and elderly men reporting sexual symptoms in the presence of moderately low total testosterone levels (<320 ng/dL), with variable levels of gonadotropins, which involves central and mostly gonadal components in its pathogenesis (16, 17).

Functional hypothalamic amenorrhea is a reversible form of GnRH deficiency, usually triggered by stressors such as excessive exercise, nutritional deficits, or psychological distress. Regardless of the specific trigger, functional hypothalamic amenorrhea is characterized by the suppression of GnRH pulsatility (18). Functional hypothalamic amenorrhea is a frequent cause of acquired female infertility, typically manifested as amenorrhea of 6-month duration or longer, low or normal gonadotropin levels, and hypoestrogenemia without organic abnormalities (19, 20). Interestingly, rare variants in the genes associated with congenital IHH were recently found in women with hypothalamic amenorrhea, suggesting that these mutations may contribute to the variable susceptibility of women to functional changes in GnRH secretion (20). Moreover, the importance of low levels of leptin, a hormone secreted by adipocytes that regulates energy homeostasis, in the pathophysiology of hypothalamic amenorrhea was clearly demonstrated by evidence of a significant improvement of the reproductive and neuroendocrine functions in women with hypothalamic amenorrhea after exogenous recombinant leptin replacement (21, 22). Although primarily a disease of females, eating disorders such as anorexia nervosa are increasingly being recognized in males and are associated with hypogonadism. Population-based studies reported that 5–15% of all patients with anorexia nervosa are males (23, 24).

Diagnostic and therapeutic strategies

Clinical presentation of HH depends on the time of onset (ie, congenital vs acquired), the severity of the defect, and the presence of associated conditions. Typically the diagnosis of congenital IHH is made during the second or third decade of life, when the patients present with delayed pubertal onset, absent or poorly developed secondary sexual characteristics, primary amenorrhea, eunuchoid proportions, or infertility. In some cases, the diagnosis may be suspected before puberty. The occurrence of micropenis and/or unilateral or bilateral cryptorchidism in boys, as well as the presence of other associated congenital abnormalities, such as midline defects, suggests congenital GnRH deficiency, especially in the context of a positive family history (25, 26). In contrast, newborn girls have no obvious abnormal findings that might provide clues to the diagnosis. Most commonly, however, the diagnosis cannot be confirmed until the expected time of puberty onset, except in the neonatal period, when gonadotropin and sexual steroid levels are expected to be elevated. The presence of anosmia is suggestive of Kallmann syndrome, and if the child is too young to undergo olfaction tests, magnetic resonance imaging (MRI) scan showing absent or abnormal olfactory bulbs or sulci strongly suggests the diagnosis. Nevertheless, it is important to note that a normal MRI does not rule out the disease because normal olfactory bulbs can be present in up to 20% of Kallmann syndrome patients (2, 3). Adult-onset HH is characterized in women by secondary amenorrhea, decreased libido, infertility, and osteoporosis; in men, symptoms of decreased libido, lack of morning erection, erectile dysfunction, inability to perform vigorous activity, depression, fatigue, and infertility are observed.

The evidence of low/normal gonadotropin levels in the setting of low concentrations of testosterone in men and estradiol in women indicates the diagnosis of HH. Rarely, selective deficiency of LH or FSH can occur due to inac-

tivating mutations of the specific β-subunits (27–29). The measurement of morning total testosterone by a reliable assay is strongly recommended in the initial diagnosis test (30). In some men, in whom total testosterone is near the lower limit of normal or in whom SHBG abnormality is suspected, measurement of free or bioavailable testosterone levels is then recommended (23). Anterior pituitary function must be investigated to rule out a more complex endocrine disorder with multiple hormone deficiencies.

Although widely used, the practical value of the GnRH test has been questionable because of its low cost-effectiveness. Indeed, the GnRH test provides no extra diagnostic information relative to baseline gonadotropin levels. In HH patients, the response to GnRH test is highly variable and depends on the severity of the gonadotropin deficiency, which is often reflected by the clinical phenotype. Similarly, the pituitary function can be first evaluated by basal hormonal levels (measured by ultrasensitive assays). Thyroid function should be assessed by TSH combined with free T_4. IGF-I can be used to evaluate the somatotropic axis, whereas secondary adrenal deficiency can be assessed by measuring a morning cortisol and ACTH. The stimulatory tests should be reserved for the situations in which the basal hormone measurements are not helpful or if there is strong clinical evidence of a multiple pituitary hormone deficiency.

Anosmia can be easily diagnosed by questioning the patient, whereas olfactometry, such as University of Pennsylvania Smell Identification Test, is necessary to determine reliably whether olfaction is normal or partially defective. Indeed, IHH patients display a broad spectrum of olfactory function, with a significant hyposmic phenotype. Accurate olfactory phenotyping in IHH subjects can inform the pathophysiology of this condition and guide genetic testing (31).

MRI of the hypothalamo-pituitary region is very useful in the management of HH. MRI can demonstrate a malformation, an expansive or infiltrative disorder of the hypothalamo-pituitary region. However, the cost-effectiveness of MRI scan to exclude pituitary and/or hypothalamic tumors is unknown according to the recent clinical practice guideline (30). Pituitary and/or hypothalamic tumors should be investigated by MRI in patients with serum testosterone less than 150 ng/dL, multiple pituitary hormone deficiency, persistent hyperprolactinemia, or symptoms of tumor mass effect (headache, visual impairment, or visual field defect). In the presence of suspected functional causes of HH, such as severe obesity, nutritional disorders, and drugs, MRI is not indicated. Additionally, MRI with specific cuts for evaluating the olfactory tract can be helpful in the diagnosis of Kallmann syndrome. Evidence of unilateral or bilateral hypoplastic/agenesis olfactory bulbs and hypoplastic anterior pituitary is pathognomonic of Kallmann syndrome.

Renal ultrasound examination is usually recommended to patients with syndromic IHH, such as Kallmann syndrome, independent of the genetic basis, although it is well known that unilateral kidney agenesis may be more prevalent in patients with *KAL1* defects. The genetic study is usually the last step in the congenital IHH investigation, and complete clinical characterization could certainly help in the gene selection. Bone mineral density of the lumbar spine, femoral neck, and hip is recommended at the initial diagnosis of HH and after 1 to 2 years of sex steroid therapy in hypogonadal patients with osteoporosis or low trauma fracture (30).

The goals of therapy for hypogonadal adolescents or young adults are the induction and maintenance of normal puberty and induction of fertility when the patient desires. testosterone therapy for adult men with symptomatic androgen deficiency is recommended to improve sexual function and sense of well-being and to increase muscle mass and strength and BMD. Testosterone is the primary treatment modality used to induce and maintain secondary sexual characteristics and sexual function in men with HH, but it does not restore fertility.

Intramuscular injections of long-acting testosterone esters (testosterone cypionate or enanthate) are commonly used. In adolescents, the initial dose of testosterone esters to induce puberty is 50–75 mg/month, which should be gradually increased every 6 months to 100–150 mg/month. The maintenance dose for adult males is 200–250 mg im every 2–3 weeks or 1000 mg of testosterone undecanoate every 3 months. Other options are transdermal preparations, including gel formulations (5–10 g/d) or 5 mg testosterone patches applied nightly over the nongenital skin (30). The long-term goals of testosterone therapy are to maintain the serum concentrations of sex steroids in the midnormal adult range. Testosterone therapy is not indicated in patients with breast or prostate cancer, a palpable prostate nodule, or indurations, or prostate-specific antigen greater than 4 ng/mL or greater than 3 ng/mL in men at high risk for prostate cancer, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, or uncontrolled or poorly controlled heart failure (30).

When fertility is desired, gonadotropin therapy is necessary to induce spermatogenesis in males with HH (32). Different treatment protocols can be used in male patients with HH. The typical gonadotropin regimen combines human chorionic gonadotropin (hCG) and FSH. One option is to combine hCG 1000 U and FSH 75 U every other day for HH patients without puberty and immature testes (<3 mL). Notably, the intra-subcutaneous route of ad-

ministration is as effective as im. The hCG doses should be titrated based on testosterone levels, targeting middle normal values. Testosterone levels usually achieve normal range values by 6 months of continuous treatment in most patients, and spermatogenesis is attained in up to 80% of the cases. Another option for patients with partial pubertal development is to start with hCG alone for 6 months and subsequently add FSH if azoospermia persists. Predictive factors of better outcome include larger testicular volume, absence of cryptorchidism, and higher serum inhibin B levels at the initial medical evaluation.

Treatment of adolescent males with exogenous hCG alone or combined with recombinant FSH for induction of puberty may result in testicular growth and hence improvement in potential fertility compared to treatment with testosterone (32). Early induction of spermatogenesis may reduce the time required for appearance of sperm and the need for prolonged cycles of gonadotropin treatment in adult life. Use of hCG alone appears to be less efficient in spermatogenesis induction and final testicular volume when compared to combined treatment with hCG and FSH (32, 33). Side effects of gonadotropin treatment include the inconvenient way of administration, gynecomastia, and the induction of antibodies to hCG, which can impair the response to hCG in the future (34, 35). It is important to note that there are few studies about the use of gonadotropins in adolescents, and most them are small case series of boys with HH who received pubertal induction with gonadotropins at various times, and thus further studies are needed.

Controversies and Areas of Uncertainty

The main and most difficult differential diagnosis of congenital IHH in boys is constitutional delay of growth and puberty. Patients with constitutional delay of puberty typically have delayed growth before puberty and delayed bone age, compatible with the height. In contrast, patients with congenital IHH have normal linear growth during childhood, and despite the absence of the pubertal growth spurt, short stature is not a common finding. The absence of long-bone epiphyseal closure explains the presence of eunuchoid proportions and relative high stature. A variety of physiological and stimulation tests have been proposed, such as LH sampling, prolactin response to various stimulating agents, gonadotropin response to GnRH, testosterone response to hCG, and daily urine excretion of FSH and LH (36). Recently, Coutant et al (37) demonstrated that a single measurement of inhibin B level discriminated IHH from constitutional delay of puberty in adolescent boys. The sensibility and specificity were 100% for inhibin B concentration of 35 pg/mL or less in boys with genital stage 1 (testis volume < 3 mL) in this study (26). Other baseline measurements (anti-Mullerian hormone, testosterone, FSH, and LH) were not useful for such discrimination.

It is notable that men with apparent isolated hypothalamic GnRH deficiency may also have primary pituitary and/or testicular defects ("a dual defect") as demonstrated by the atypical responses to long-term exogenous pulsatile GnRH treatment (43). The pituitary and/or testicular defects may be initially masked by the GnRH deficiency in these patients. Therefore, the pathophysiology of hypogonadism in a subgroup of patients with IHH could be more complex than previously thought and possibly not limited to an isolated hypothalamic or pituitary defect.

Interestingly, sustained reversal of hypogonadism has been observed in about 10% of congenital IHH patients after discontinuation of treatment. To date, the triggers leading to reversal of IHH are not well understood. Androgen exposure has been suggested to predispose to reversal, and specific genetic backgrounds are especially prone to reversal HH (38). The reversible form of HH should be suspected if testicular volume increases during testosterone administration or in the absence of endocrine therapy. A brief discontinuation of hormonal therapy to assess reversibility is rational in patients with HH. However, the reversibility may not always be lifelong. Interestingly, heterogeneous genetic background (*FGFR1*, *PROK2*, *GNRH*, *CHD7*, and *TAC/TACR3* mutations) has been associated with reversal of congenital HH (38).

Testosterone replacement in older men is another controversial issue in the practice of medicine. Despite the long existence of testosterone as a pharmaceutical medication, few large-scale, double-blind, placebo-controlled, multiple end point studies had been performed on testosterone therapy in men. In fact, older men are more susceptible to risks from testosterone intervention, such as benign prostatic hyperplasia, prostate cancer, and cardiovascular disease. In addition, many men in the middle to older age group do not fit the simple definition of either primary or secondary hypogonadism but have a mixed type of testosterone deficiency with impairment of both testicular and hypothalamic pituitary signals, indicating that the pathogenesis of low testosterone in this group is not well defined (39, 40).

Returning to the Patient

Low gonadotropin and estradiol levels resulting in primary amenorrhea and poor pubertal development suggested the diagnosis of a severe form of HH in this young

lady. The normal remaining pituitary function indicated an isolated form of HH. Her history and physical examination ruled out functional hypothalamic amenorrhea. Central anatomic defects and systemic diseases were excluded by routine tests and a normal brain imaging. The early presentation of the hypogonadism, manifesting as primary amenorrhea, and the association with nonreproductive phenotypes (ogival palate and bone abnormalities) contributed to the hypothesis of a congenital defect in this apparently sporadic case of IHH. Additionally, the normal olfaction test confirmed the diagnosis of idiopathic normosmic IHH. More recently, systematic genetic screening revealed a large heterozygous deletion of *FGFR1* in this female with IHH (41).

The case depicted here illustrates the typical clinical presentation of severe female GnRH deficiency. Shaw et al (42) recently demonstrated that the clinical presentation of women with GnRH deficiency can vary from primary amenorrhea and absence of any secondary sexual characteristics to spontaneous breast development and occasional menses. In this large series of women with GnRH deficiency, most patients exhibited some degree of breast development (51%), and a small percentage experienced isolated menses (10%). Hypogonadal women with spontaneous thelarche were more likely to have undergone pubarche, suggesting that aromatization of adrenal androgens could contribute to breast development.

Young women with HH are at risk for bone loss and fracture. Congenital hypogonadism may be particularly detrimental to the skeleton because it may lead to failure to achieve peak bone mass, in addition to loss of established bone mass. Estrogen-progesterone replacement, calcium and vitamin D supplementation, and nutritional counseling should be provided. Multiple formulations of estrogen are available and include oral estradiol, oral conjugated estrogen, transdermal estrogen patches, and gel. In patients who have not yet started pubertal development, estrogen therapy should be started at low doses (5 μg ethinyl estradiol, 0.3 mg conjugated equine estrogen, or 0.5 mg micronized estradiol daily) to promote breast development. After 6 months or when breakthrough bleeding occurs, cyclical therapy can be initiated by adding a progestogen, and the dose of estrogen is gradually increased over a 2- to 3-year period. Full replacement dose of estrogen and progesterone is attained with 0.625–1.25 mg conjugated equine estrogen daily combined with cyclic 5–10 mg medroxyprogesterone acetate or 200 mg oral micronized progesterone. Other estrogen options are daily 2 mg micronized estradiol orally, 100–200 μg transdermal 17β-estradiol patches or 1–2 mg estrogen gel. Alternatively, combined contraceptive pills, usually containing ethinyl estradiol, can be conveniently used. However, natural estrogens are preferable to synthetic estrogens because of incomplete metabolization and a greater risk of thromboembolism and arterial hypertension of the synthetic forms. In patients in whom fertility is desired, induction of gonadotropin secretion by pulsatile GnRH or treatment with exogenous gonadotropin is the current hormonal treatment of choice.

Conclusions

Maestre de San Juan was the first to report, in 1856, the association of the absence of olfactory structures in the brain and the presence of small testes in an individual. Although this description took place more than a century ago, the genetics and natural history of Kallmann syndrome are still incompletely understood. Similarly, testosterone has been available as a pharmaceutical medication since 1930, and it has been used since then to treat failure of male secondary sexual development. Definitely, there are still numerous controversial issues in the practice of medicine, requiring individual good sense for taking decisions regarding whom, when, and how to treat. Long-term and well-controlled studies are necessary to solve the current uncertainties in the field of reproductive disorders.

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Address all correspondence and requests for reprints to: Ana Claudia Latronico, Av. Dr. Enéas de Carvalho Aguiar 255, 7 andar, sala 7037, CEP 05403-000, São Paulo, São Paulo, Brazil. E-mail: anaclusp@gmail.com.

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References

1. **Seminara SB, Hayes FJ, Crowley WF Jr.** Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations. *Endocr Rev*. 1998;19:521–539.
2. **Silveira LF, MacColl GS, Bouloux PM.** Hypogonadotropic hypogonadism. *Semin Reprod Med*. 2002;20:327–338.
3. **Mitchell AL, Dwyer A, Pitteloud N, Quinton R.** Genetic basis and variable phenotypic expression of Kallmann syndrome: towards a unifying theory. *Trends Endocrinol Metab*. 2011;22:249–258.
4. **Schwanzel-Fukuda M, Bick D, Pfaff DW.** Luteinizing hormone-releasing hormone (LHRH)-expressing cells do not migrate normally in an inherited hypogonadal (Kallmann) syndrome. *Brain Res Mol Brain Res*. 1989;6:311–326.
5. **Wray S, Grant P, Gainer H.** Evidence that cells expressing luteinizing hormone-releasing hormone mRNA in the mouse are derived from

progenitor cells in the olfactory placode. *Proc Natl Acad Sci USA*. 1989;86:8132–8136.
6. **Quinton R, Duke VM, Robertson A, et al.** Idiopathic gonadotrophin deficiency: genetic questions addressed through phenotypic characterization. *Clin Endocrinol (Oxf)*. 2001;55:163–174.
7. **Fromantin M, Gineste J, Didier A, Rouvier J.** [Impuberism and hypogonadism at induction into military service. Statistical study]. *Probl Actuels Endocrinol Nutr*. 1973;16:179–199.
8. **Silveira LF, Trarbach EB, Latronico AC.** Genetics basis for GnRH-dependent pubertal disorders in humans. *Mol Cell Endocrinol*. 2010;324:30–38.
9. **Young J, Metay C, Bouligand J, et al.** SEMA3A deletion in a family with Kallmann syndrome validates the role of semaphorin 3A in human puberty and olfactory system development. *Hum Reprod*. 2012;27:1460–1465.
10. **Semple RK, Topaloglu AK.** The recent genetics of hypogonadotrophic hypogonadism—novel insights and new questions. *Clin Endocrinol (Oxf)*. 2010;72:427–435.
11. **Topaloglu AK, Tello JA, Kotan LD, et al.** Inactivating KISS1 mutation and hypogonadotropic hypogonadism. *N Engl J Med*. 2012;366:629–635.
12. **Pitteloud N, Quinton R, Pearce S, et al.** Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. *J Clin Invest*. 2007;117:457–463.
13. **Sykiotis GP, Plummer L, Hughes VA, et al.** Oligogenic basis of isolated gonadotropin-releasing hormone deficiency. *Proc Natl Acad Sci USA*. 2010;107:15140–15144.
14. **Nachtigall LB, Boepple PA, Pralong FP, Crowley WF Jr.** Adult-onset idiopathic hypogonadotropic hypogonadism—a treatable form of male infertility. *N Engl J Med*. 1997;336:410–415.
15. **Dwyer AA, Hayes FJ, Plummer L, Pitteloud N, Crowley WF Jr.** The long-term clinical follow-up and natural history of men with adult-onset idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2010;95:4235–4243.
16. **Wu FC, Tajar A, Beynon JM, et al.** Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010;363:123–135.
17. **Tajar A, Huhtaniemi IT, O'Neill TW, et al.** Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *J Clin Endocrinol Metab*. 2010;97:1508–1516.
18. **Santoro N, Filicori M, Crowley WF Jr.** Hypogonadotropic disorders in men and women: diagnosis and therapy with pulsatile gonadotropin-releasing hormone. *Endocr Rev*. 1986;7:11–23.
19. **Gordon CM.** Clinical practice. Functional hypothalamic amenorrhea. *N Engl J Med*. 2010;363:365–371.
20. **Caronia LM, Martin C, Welt CK, et al.** A genetic basis for functional hypothalamic amenorrhea. *N Engl J Med*. 2011;364:215–225.
21. **Welt CK, Chan JL, Bullen J, et al.** Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med*. 2004;351:987–997.
22. **Chou SH, Chamberland JP, Liu X, et al.** Leptin is an effective treatment for hypothalamic amenorrhea. *Proc Natl Acad Sci USA*. 2011;108:6585–6590.
23. **Lucas AR, Beard CM, O'Fallon WM, Kurland LT.** 50-Year trends in the incidence of anorexia nervosa in Rochester, MN: a population-based study. *Am J Psychiatry*. 1991;148:917–922.
24. **Robergeau K, Joseph J, Silber TJ.** Hospitalization of children and adolescents for eating disorders in the State of New York. *J Adolesc Health*. 2006;39:806–810.
25. **Semple RK, Achermann JC, Ellery J, et al.** Two novel missense mutations in g protein-coupled receptor 54 in a patient with hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2005;90:1849–1855.
26. **Han TS, Bouloux PM.** What is the optimal therapy for young males with hypogonadotropic hypogonadism? *Clin Endocrinol (Oxf)*. 2010;72:731–737.
27. **Lofrano-Porto A, Barra GB, Giacomini LA, et al.** Luteinizing hormone β mutation and hypogonadism in men and women. *N Engl J Med*. 2007;357:897–904.
28. **Layman LC, Lee EJ, Peak DB, et al.** Delayed puberty and hypogonadism caused by mutations in the follicle-stimulating hormone β-subunit gene. *N Engl J Med*. 1997;337:607–611.
29. **Layman LC, Porto AL, Xie J, et al.** FSH β gene mutations in a female with partial breast development and a male sibling with normal puberty and azoospermia. *J Clin Endocrinol Metab*. 2002;87:3702–3707.
30. **Bhasin S, Cunningham GR, Hayes FJ, et al.** Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95:2536–2559.
31. **Lewkowitz-Shpuntoff HM, Hughes VA, Plummer L, et al.** Olfactory phenotypic spectrum in idiopathic hypogonadotropic hypogonadism: pathophysiological and genetic implications. *J Clin Endocrinol Metab*. 2012;97:E136–E144.
32. **Zacharin M, Sabin MA, Nair VV, Dagabdhao P.** Addition of recombinant follicle-stimulating hormone to human chorionic gonadotropin treatment in adolescents and young adults with hypogonadotropic hypogonadism promotes normal testicular growth and may promote early spermatogenesis. *Fertil Steril*. 2012;98:836–842.
33. **Barrio R, de Luis D, Alonso M, Lamas A, Moreno JC.** Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. *Fertil Steril*. 1999;71:244–248.
34. **Thau RB, Goldstein M, Yamamoto Y, Burrow GN, Phillips D, Bardin CW.** Failure of gonadotropin therapy secondary to chorionic gonadotropin-induced antibodies. *J Clin Endocrinol Metab*. 1988;66:862–867.
35. **Delemarre EM, Felius B, Delemarre-van de Waal HA.** Inducing puberty. *Eur J Endocrinol*. 2008;159(suppl 1):S9–S15.
36. **Segal TY, Mehta A, Anazodo A, Hindmarsh PC, Dattani MT.** Role of gonadotropin-releasing hormone and human chorionic gonadotropin stimulation tests in differentiating patients with hypogonadotropic hypogonadism from those with constitutional delay of growth and puberty. *J Clin Endocrinol Metab*. 2009;94:780–785.
37. **Coutant R, Biette-Demeneix E, Bouvattier C, et al.** Baseline inhibin B and anti-Mullerian hormone measurements for diagnosis of hypogonadotropic hypogonadism (HH) in boys with delayed puberty. *J Clin Endocrinol Metab*. 2010;95:5225–5232.
38. **Raivio T, Falardeau J, Dwyer A, et al.** Reversal of idiopathic hypogonadotropic hypogonadism. *N Engl J Med*. 2007;357:863–873.
39. **Cunningham GR, Toma SM.** Clinical review: why is androgen replacement in males controversial? *J Clin Endocrinol Metab*. 2011;96:38–52.
40. **Swerdloff R, Wang C.** Testosterone treatment of older men—why are controversies created? *J Clin Endocrinol Metab*. 2011;96:62–65.
41. **Trarbach EB, Teles MG, Costa EM, et al.** Screening of autosomal gene deletions in patients with hypogonadotropic hypogonadism using multiplex ligation-dependent probe amplification: detection of a hemizygosis for the fibroblast growth factor receptor 1. *Clin Endocrinol (Oxf)*. 2010;72:371–376.
42. **Shaw ND, Seminara SB, Welt CK, et al.** Expanding the phenotype and genotype of female GnRH deficiency. *J Clin Endocrinol Metab*. 2011;96:E566–E576.
43. **Sykiotis GP, Hoang XH, Avbelj M, et al.** Congenital idiopathic hypogonadotropic hypogonadism: evidence of defects in the hypothalamus, pituitary, and testes. *J Clin Endocrinol Metab*. 2010;95(6):3019–3027.