Hypogonadotropic Hypogonadism

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KEYWORDS

• Delayed puberty • Hypogonadotropic hypogonadism • Amenorrhea

KEY POINTS

- Delayed puberty is defined as absent testicular enlargement in boys or breast development in girls at an age that is 2 to 2.5 SDS later than the mean age at which these events occur in the population (traditionally, 14 years in boys and 13 years in girls).
- Hypogonadotropic hypogonadism (HH) can be classified into four major categories: congenital HH (CHH) with anosmia; CHH without anosmia; acquired/functional HH; and pituitary-dependent gonadotropin deficiency.
- The overarching goal of HH treatment in males is to mimic endogenous puberty in younger boys with known HH or to induce more rapid development of male secondary sex characteristics in older boys.
- With appropriate hormone replacement therapy, female patients with HH can develop secondary sexual characteristics, maintain normal sex steroid concentrations, and lead healthy sexual lives.
- With appropriate treatment, men and women with HH may be able to achieve fertility.

INTRODUCTION

Puberty consists of two components: gonadarche and adrenarche. Gonadarche reflects reactivation of the hypothalamic gonadotropin releasing hormone (GnRH) pulse generator, characterized by increased pulsatile secretion of GnRH from the hypothalamus. This promotes pulsatile pituitary gonadotropin secretion which, in turn, stimulates the growth and maturation of the gonads accompanied by increasing gonadal sex steroid secretion. Adrenarche refers to pubertal adrenal maturation, manifested by pubarche which is the development of pubic and axillary hair. As adrenarche is independent of gonadarche, its absence is excluded from the definition of delayed

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puberty. The age at onset of puberty may be associated with health consequences later in adulthood. As would be anticipated, later age at menarche is associated with increased risks for osteopenia and osteoporotic fractures in women, possibly due to shorter duration of estrogen exposure.[1]

Studies of twins have shown that the timing of puberty is highly heritable. Epidemiologic data suggest that approximately 50% to 75% of the variation in the age at onset of puberty is influenced by genetics.[2] Other factors such as nutrition, metabolism, environment, and general health can also influence the onset and tempo of puberty. Delayed puberty is traditionally defined as a lack of testicular enlargement $\geq$4 mL in boys or breast development in girls at an age that is 2 to 2.5 SD later than the mean age at which these events occur in the population (traditionally, 14 years in boys and 13 years in girls),[3] or based on puberty nomograms in some populations.[4] The lack of menarche by age 16 years or by 3 years post-thelarche is considered abnormal. Some children show initial pubertal maturation yet fail to complete puberty.[5]

One cause of delayed/absent puberty is hypogonadotropic hypogonadism (HH), which refers to inadequate hypothalamic/pituitary function leading to deficient production of sex steroids in males and females. Individuals with HH typically have normal gonads, and thus HH differs from hypergonadotropic hypogonadism, which is associated with primary gonadal insufficiency. HH may be congenital or acquired and is distinct from constitutional delay of growth and puberty (CDGP).[6] Although HH can rarely be transient or intermittent, CDGP is transient by definition and is considered to be a variant of normal development (see Jennifer Harrington's article, "Delayed Puberty Including Constitutional Delay: Differential and Outcome," in this issue). The exact incidence of HH is unclear, likely due to ascertainment bias and missed diagnosis. To understand the disorders leading to inadequate hypothalamic/pituitary function, a review of the development of the GnRH neuronal system and components of the hypothalamic pituitary gonadal axis (HPG) axis is germane as discussed in the following.

ONTOGENY OF GnRH NEURONS

Reproductive competence depends on the proper development of the GnRH neuron system. In the human fetus, GnRH neurons initially develop in the olfactory placode outside the central nervous system. Subsequently, accompanied by olfactory-derived axons, olfactory epithelial sheath cells, and blood vessels, the GnRH neurons migrate toward the cribriform plate. Migration of the GnRH neurons seems to pause at the nasal/forebrain junction before crossing the cribriform plate. During this "pause" phase, multiple tissues, chemokines, growth factors, and neurotransmitters seem to form gradients influencing movement of GnRH neurons. On reaching the hypothalamus, the GnRH neurons disperse to their final locations, sending projections to the median eminence.[7]

The precise origin and specific factors responsible for the specification, differentiation, connectivity, and stabilization of GnRH neurons remain enigmatic.[8]

COMPONENTS OF THE HPG AXIS

The human hypothalamus contains approximately 2000 diffusely distributed GnRH neurons. The mammalian GnRH neuron displays unique characteristics.[9] At the median eminence, their dendritic fibers are intertwined, encased by tanycytes (specialized ependymal cells of the third ventricle), project to blood vessels, and receive synaptic inputs.[10] At the median eminence, the GnRH neurons intermittently discharge GnRH into the primary plexus of the hypophysial portal circulation, stimulating pulsatile leutinizing hormone (LH) and follicle stimulating hormone (FSH) secretion. Generally, GnRH pulses correspond 1:1 with LH pulses.

The GnRH neurons are physically located within a neuronal network secreting three neuropeptides: kisspeptin, neurokinin B, and dynorphin. These neurons, labeled the kisspeptin-neurokinin B-dynorphin (KNDy) neurons, are in close proximity to glial cells such as tanycytes, astrocytes, and ependymal cells. The KNDy neurons in the infundibular nucleus of the hypothalamus seem to comprise the major elements of the GnRH pulse generator, with kisspeptin and neurokinin B partaking in major facets of GnRH secretion.

Gonadotropin-releasing hormone is a decapeptide (pGlu-His-Trp-Ser-Trp-Gly-Leu-Arg-Pro-Gly-NH_2) derived from a 92-amino acid precursor, prepro-GnRH, originally characterized in 1984.[11] LH and FSH are synthesized in the same gonadotroph cells in the anterior pituitary. LH and FSH are glycoproteins with identical alpha subunits and distinct beta subunits that confer hormone specificity. Glycosylation seems to influence hormone stability, circulating serum half-life, protein folding, cellular trafficking, and receptor signaling. The patterns of gonadotropin secretion prenatally and postnatally and their relationships to the gonadal steroids, testosterone and estradiol, have been well characterized. In adult men, pulse frequency is relatively constant at approximately one pulse every 90 to 120 minutes. Among women, pulse frequency varies across the menstrual cycle from approximately one pulse per hour during the follicular phase and one pulse every 180 minutes during the luteal phase.[12] The actions of LH and FSH are mediated by their cognate seven-transmembrane domain G protein-coupled receptors, the luteinizing hormone/choriogonadotropin receptor (LHCGR) and FSH receptor, respectively.

Reproduction is metabolically costly, requiring ample energy reserve to support the onset of puberty and maintenance of fertility. Energy reserves are signaled in part by leptin release from adipose tissue. Patients with leptin deficiency manifest delayed puberty that resolves with leptin treatment.[13] Although initially conceptualized as the proximate factor initiating puberty, leptin functions as an obligatory permissive factor for pubertal development that informs the hypothalamus of overall energy status. Much remains to be discovered about how the hypothalamic network monitors energy balance and transmits information to the GnRH pulse generator to influence kisspeptin secretion.[14]

CLASSIFICATION OF HYPOGONADOTROPIC HYPOGONADISM

HH can be classified into four major categories: (1) congenital HH (CHH) with anosmia; (2) CHH without anosmia; (3) acquired/functional HH; and (4) pituitary-dependent gonadotropin deficiency. However, it has become apparent that phenotypic heterogeneity exists for anosmia; the extent of anosmia can vary among family members within a single family. Additional subclassifications include genetic, anatomic, or functional. Self-limited delayed puberty, also known as constitutional delay, is discussed in Jennifer Harrington's article, "Delayed Puberty Including Constitutional Delay: Differential and Outcome," in this issue.

CONGENITAL HYPOGONADOTROPIC HYPOGONADISM

In many instances, CHH is due to deficient production, secretion, or action of gonadotropin-releasing hormone (GnRH) and is characterized by incomplete or absent puberty in the setting of low gonadotropin and sex steroid concentrations. Given the developmental origins of GnRH neurons in the olfactory placode, CHH may be associated with anosmia (absent sense of smell) or hyposmia (reduced sense of smell). This association is known as Kallmann syndrome. CHH can present as isolated congenital GnRH deficiency or can be syndromic. Syndromic CHH is associated with

other developmental anomalies (Table 1). In some instances, HH may be associated with additional anterior pituitary hormone deficiencies.

Prenatal testicular testosterone secretion is crucial for the development of the external genital structures in boys. Boys with CHH may present with micropenis because fetal penile growth typically occurs after the 12th week of gestation when external genital differentiation has been completed. In other words, boys with CHH generally do not have otherwise atypical external genitalia. The explanation for this finding is that human chorionic gonadotropin (hCG) drives fetal testicular testosterone secretion early during gestation when the initial development of the external genitalia occurs. The pituitary gland begins to secrete gonadotropins during the second trimester, with LH and FSH becoming detectable in fetal blood after 14 weeks of gestation.

Genetics of Hypogonadotropic Hypogonadism

The recognition that HH was associated with deleterious GnRH receptor variants fueled the ongoing pursuit to identify genes associated with altered HPG function.[15] Inheritance patterns include autosomal dominant, autosomal recessive, X-linked, and oligogenic. An oligogenic pattern refers to the presence of concomitant variants in several different genes, leading to a CHH phenotype. To date, more than 50 such genes have been identified. Genome-wide association studies continue to expand knowledge regarding genes associated with CHH (Fig. 1). These genes may be classified as being associated with anosmia/hyposmia (Kallmann syndrome) or normosmia (Table 2). The classic example of anosmic CHH is X-linked Kallmann syndrome due to anosmin-1 (*ANOS1*) variants. The absence of this protein prevents migration of GnRH neurons to the hypothalamus. Additional features of *ANOS1* mutations include unilateral renal agenesis, sensorineural hearing loss, dental agenesis, synkinesia (alternating mirror movements), and cleft lip/palate.

Some genetic variants have additional findings. Defects in *NROB1* encoding the DAX1 protein are associated with CHH and congenital adrenal hypoplasia. The

Table 1
Syndromic causes of congenital hypogonadotropic hypogonadism

Gene	Syndrome
Several genes including *HESX1, PROP1, LHX3,* and *LHX4*	Septo-optic dysplasia/panhypopituitarism
Loss of paternal 15q11.2	Prader–Willi syndrome
CHD7	CHARGE syndrome
Several genes including *BBS1, BBS10, BBS2, BBS9, MKKS, BBS12, MKS1, BBS4, BBS7, BBS7,* and *TTC8*	Bardet–Biedl syndrome
SOX10	Waardenburg syndrome
OTUD4, PNPLA6, RNF216, STUB1	Gordon Holmes syndrome
HFE	HFE-associated hereditary hemochromatosis
TUBB3	TUBB3 E410 K syndrome
RAB3GAP1, RAB3GAP2, RAB18, TBC1D20	Warburg micro syndrome/Martsolf syndrome
Xp21 microdeletion encompassing NROB1 (DAX1) and DMD	Xp21 deletion syndrome
Xp22.3 microdeletion encompassing ANOS1	Xp22.3 deletion syndrome
IGSF1	X-linked with central hypothyroidism, macroorchidism

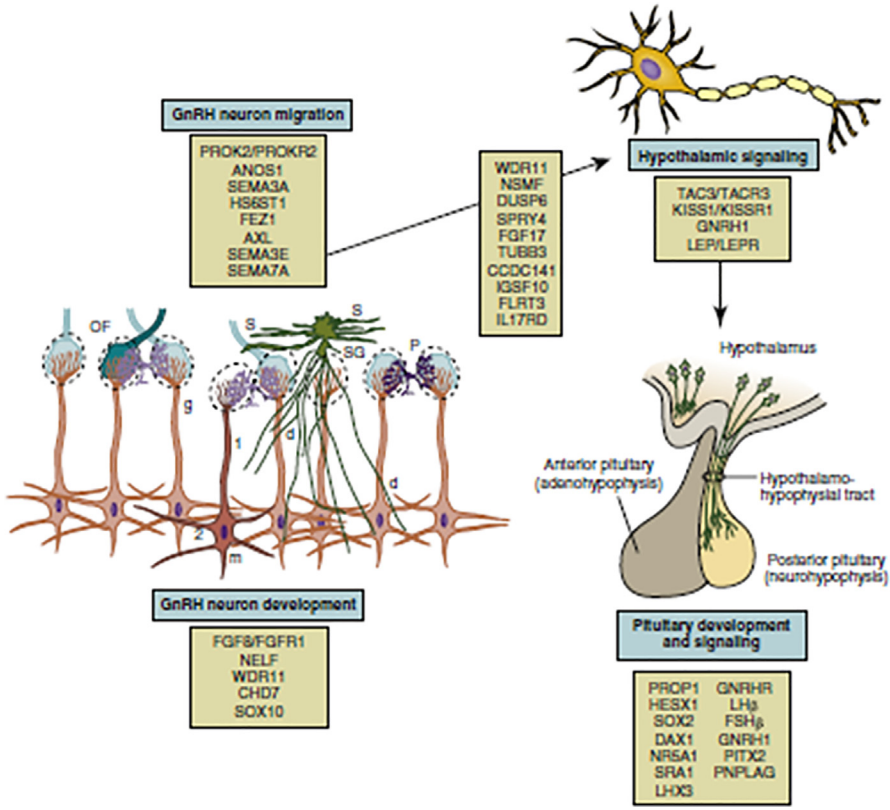

Fig. 1. Genes in GnRH neuron development. Illustration showing genes and roles in GnRH neuron and pituitary development. (Reprinted with permission: Oberfield SE, Witchel SF. In Strauss JF, Barbieri RL, Dokras A, Williams CJ, Williams SZ, eds. Yen and Jaffe's Reproductive Endocrinology, 9th ed. Elsevier, Philadelphia, 2023.)

CHARGE syndrome, characterized by coloboma, heart anomalies, choanal atresia, growth retardation, and genital and ear anomalies, is due to variants in *CHD7* that may lead to isolated CHH or CHH associated with other clinical features.

PITUITARY HORMONE DEFICIENCY

Gonadotropin deficiency can occur in patients with combined pituitary hormone deficiency (CPHD). Some patients also have septo-optic dysplasia. Typically, genetic variants associated with CPHD are involved in development of the head or pituitary gland development. Specific genes associated with CPHD include *LHX4*, *HESX1*, *PITX3*, *GATA2*, *PROP1*, and *SOX2*. Detailed discussion of these genes can be found elsewhere.[16] Inactivating variants of the specific β-subunits of LH and FSH have been described.[17] Ig superfamily member 1 (IGSF1) deficiency is an X-linked disorder associated with central hypothyroidism, macroorchidism, and delayed puberty.[18]

ACQUIRED HYPOGONADISM

Acquired HH reflects central nervous system (CNS) dysfunction associated with trauma, tumor, infection, or another intracranial processes (**Box 1**). Craniopharyngiomas and

Table 2
Inheritance pattern of genes associated with congenital hypogonadotropic hypogonadism

Gene	Product	Olfactory Function	Inheritance Pattern
ANOS1/KAL1	Anosmin-1	Anosmic	X-linked
SEMA3A	Semaphorin 3A	Anosmic	AD with variable expression
SOX10	Sex-determining region Y-Box 10 transcription factor	Anosmic	AD with variable expression
IL17RD	Interleukin-17 receptor D	Anosmic	AD with variable expression/AR
FEZF1	FEZ family zinc finger 1	Anosmic	AR
FGFR1	Fibroblast growth factor receptor 1	Anosmic or normosmic	AD with variable expression
FGF8	Fibroblast growth factor 8	Anosmic or normosmic	AD with variable expression
KLB	β-Klotho	Anosmic or normosmic	AD with variable expression
PROK2 and PROKR2	Prokineticin 2 and its receptor	Anosmic or normosmic	AR/oligogenic
CHD7	Chromodomain helicase DNA-binding protein 7	Anosmic or normosmic	AD with variable expression
NSMF	N-methyl-D-aspartate receptor synaptonuclear signaling and neuronal migration factor	Anosmic or normosmic	Oligogenic
HS6ST1	Heparin sulfate 6-o-sulfotransferase 1	Anosmic or normosmic	Autosomal dominant/oligogenic
FGF17	Fibroblast growth factor 17	Anosmic or normosmic	Autosomal dominant/oligogenic
SPRY4	Sprouty homolog 4	Anosmic or normosmic	Autosomal dominant/oligogenic
DUSP6	Dual specificity phosphatase 6/MKP3-mitogen-activated protein kinase phosphatase	Anosmic or normosmic	Autosomal dominant/oligogenic
FLRT3	Fibronectin leucine rich transmembrane protein 3	Anosmic or normosmic	Indeterminate/oligogenic
WDR11	WD repeat-containing protein 11	Anosmic or normosmic	Indeterminate/oligogenic
AXL	AXL receptor tyrosine kinase	Anosmic or normosmic	Indeterminate/oligogenic
GNRHR	GnRH receptor	Normosmic	Autosomal recessive
GNRH1	Prepro-GnRH	Normosmic	Autosomal recessive
KISS1R	Kisspeptin receptor 1	Normosmic	Autosomal recessive
KISS1	Kisspeptin	Normosmic	Autosomal recessive
TAC3	Neurokinin B	Normosmic	Autosomal recessive
TAC3R	Neurokinin B receptor	Normosmic	Autosomal recessive

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

Box 1
Causes of acquired secondary hypogonadism

- Intracranial space-occupying lesions (eg, tumors/cysts)
- Infiltrative disease (eg, histiocytosis, sarcoidosis, or hemochromatosis)
- Infection (eg, meningitis)
- Pituitary apoplexy (bleeding into pituitary gland)
- Pituitary adenoma
- Rathke's cleft cyst
- CNS trauma
- CNS irradiation
- Chemotherapy
- Chronic disease (eg, diabetes, anorexia, obesity, and chronic kidney disease)
- Excessive exercise
- Critical illness
- Chronic opioid, glucocorticoid, or anabolic steroid use
- Hyperprolactinemia, prolonged hypothyroidism

germ cell tumors can disrupt the hypothalamic–pituitary stalk or directly impact pituitary function to inhibit gonadotropin production. Intracranial surgeries and/or cranial radiation therapy greater than 30 Gy are known risk factors for HH. Moderate to severe trauma to the brain can induce hypothalamic–pituitary dysfunction. Inflammatory, autoimmune, and infiltrative diseases of the pituitary gland are rare causes of acquired HH. Curiously, hemochromatosis preferentially affects gonadotrophs resulting in isolated HH.

FUNCTIONAL

Functional HH reflects the hypothalamic response to intense physical activities, intense emotional stress, nutrition–caloric deficiency, or chronic systemic illness.[19] Chronic systemic illnesses associated with delayed or arrested puberty include inflammatory bowel disease, cystic fibrosis, sickle cell anemia, thalassemia, hypothyroidism, restrictive eating disorder, and poorly controlled type 1 diabetes mellitus, among others. Typically, effective treatment of the underlying disorder is associated with pubertal progression and reversibility of the functional HH.

Peripheral signals such as leptin convey information about nutritional status to indirectly modulate GnRH neurosecretion. Indeed, the reproductive phenotype of inactivating variants involving leptin or its receptor emphasizes the importance of adequate nutritional status for HPG axis function.

Acquired HH can also be caused by drugs, infiltrative or infectious pituitary lesions, hyperprolactinemia, brain trauma, pituitary/brain radiation, and systemic diseases such as hemochromatosis, sarcoidosis, or histiocytosis.

DIAGNOSIS OF HYPOGONADOTROPIC HYPOGONADISM

CHH may be diagnosed in males as cryptorchidism with or without micropenis during the mini-puberty of infancy (a period of transient re-activation of the HPG axis) or in adolescence when patients fail to develop pubertal changes. HH is typically a

diagnosis of exclusion after confirming the absence of structural changes or acquired conditions. For some children with syndromic HH, accompanying signs and symptoms often point to HH. If the adolescent presents with any neurologic symptoms (eg, headache, visual disturbances, recurrent emesis) or signs (eg, focal deficits, visual field defects), brain imaging must be completed.

Distinguishing HH from constitutional delay may be challenging. Some patients with HH participate in a diagnostic odyssey involving multiple health care providers and medical testing. Further, the traditional approach of "watchful waiting" may hinder the diagnostic process and negatively impact psychosocial health. Like those with other rare disorders, individuals with CHH may feel different and isolated from peers. Speculation regarding potential infertility/subfertility may elicit added distress for the patient and extended family.[20] Genetic testing has become increasingly available and may be helpful because the genetic architecture differs between HH and CDGP.[21]

TREATMENT OF HYPOGONADOTROPIC HYPOGONADISM IN MALES

The overarching goal of HH treatment is to mimic endogenous puberty in younger boys with known HH or to induce more rapid development of male secondary sex characteristics in older boys. Induction of normal age-appropriate body composition, bone density, and psychosocial functioning are other important goals.

Timing of Treatment

In some cases, HH is detected early in life because of small phallic size and an absent mini-puberty of infancy. When it is certain that spontaneous puberty will not occur, the timing of pubertal induction should generally match the boy's peers or family history. More commonly, HH is not confirmed in infancy but may be possible based on patients' underlying diagnoses or treatments. In these cases, because there is no accepted diagnostic test for HH in peripubertal boys, watchful waiting is the first-line approach to exclude a simple delay in puberty. If testicular enlargement has not occurred by an arbitrary age, usually 14 years, there is a higher suspicion of HH, and treatment should begin. In older boys with acquired HH who have already begun puberty, treatment can commence once the diagnosis is confirmed.

Approaches to Treatment

Testosterone esters

Historically, treatment of HH in both early and later adolescence has been with injectable testosterone esters, usually testosterone cypionate, enanthate, or propionate. These preparations have a long track record of safety and efficacy and are inexpensive and easy to administer. Injectable testosterone reliably increases secondary sex characteristics such as penile enlargement, development of male-typical facial and body hair, linear growth, weight gain, deepening of the voice, and increased muscularity. However, it does not change testicular volume, which depends on gonadotropin secretion, particularly FSH. Similarly, it does not promote spermatogenesis, which requires both gonadotropins and high intra-testicular testosterone concentrations.[22] In addition, serum testosterone concentrations are elevated for several days after each injection but may reach subnormal trough levels before the next injection.

There are many other testosterone preparations available[23] that have been developed for use in adult men. Transdermal testosterone gels have become popular and avoid the need for injections and permit more stable testosterone concentrations. However, they require daily use and carry a risk for inadvertent transfer of testosterone

to children and women. Oral testosterone undecanoate has been used for short-term treatment of constitutional delay of growth but is not yet generally recommended for pubertal induction in HH.[24] Testosterone esters may be injected subcutaneously, which decreases injection pain and maintains satisfactory pharmacokinetics.[25]

Several testosterone regimens have been proposed.[23] A common approach is a starting dose of injectable testosterone cypionate or enanthate of 50 mg monthly, increasing by 50 mg every 6 months to attain an adult dose of 150 to 250 mg every 2 to 4 weeks. Transdermal testosterone gel can be started at 10 mg of delivered testosterone every other day, with gradual increases over 2 to 3 years to reach an adult dose of 40 to 80 mg of delivered testosterone every day. Responsiveness varies, and some patients may require faster or slower advances. After reaching adult doses, serum testosterone levels may be monitored periodically. This may be done midway between injectable testosterone doses or before a dose as a trough level. In patients using transdermal testosterone gel, serum levels can be monitored at any time, as concentrations are stable over the course of the day.[26]

Gonadotropins

An alternative approach that is gaining popularity is the use of injectable gonadotropins to induce testicular maturation and growth, with the aim of promoting both endogenous testosterone secretion and Sertoli cell growth. This approach has been shown to stimulate spermatogenesis and increase the long-term chance of fertility.[27] Testicular growth may also confer psychological benefit for the patient. hCG, which stimulates the LH receptor, has been used alone or with recombinant FSH (rFSH) for this purpose.[23,28] In patients with known HH, gonadotropin therapy can be used until testicular growth and physical maturation have occurred, and the regimen can then be changed to testosterone for long-term maintenance. The collection of a semen sample at the completion of combination therapy can be considered.

Fertility in men with congenital hypogonadotropic hypogonadism: Use of gonadotropins

Many regimens have been published for gonadotropin stimulation that vary by the order of administration and the doses used. Many regimens call for a period of FSH treatment lasting for 1 to 12 months, following which hCG is added for 6 to 24 months to induce endogenous testosterone secretion and subsequent virilization.[23] This initial treatment with rFSH alone is predicted to lead to better Sertoli cell and testicular growth than hCG alone or combined with rFSH because testosterone exposure, either by direct testosterone administration or by hCG stimulation, may cause premature cessation of Sertoli cell proliferation.[29] Although gonadotropin treatment has advantages over testosterone treatment, it is burdensome for patients, requiring multiple injections weekly, and it may be difficult for some teens to complete. Similar regimens replicating endocrine regulation of spermatogenesis or exogenous gonadotropins may be used to induce fertility in adult men following initial testosterone treatment.[30] However, treatment tends to be more successful in men with acquired HH than those with CHH.[29]

Adverse Effects of Testosterone Treatment

Testosterone treatment in adolescent boys is generally safe. Gynecomastia is common in the untreated HH population, but testosterone administration may increase the incidence due to aromatization of testosterone to estradiol. Priapism occurs rarely in boys receiving testosterone. Dose-related increases in hematocrit are common, and routine monitoring of this is recommended after adult testosterone doses are reached.[31] Behavioral problems may arise but are usually manageable in neurotypical

individuals. Adverse behaviors may require dose reduction, especially in those with neurocognitive disabilities.

TREATMENT OF HYPOGONADOTROPIC HYPOGONADISM IN FEMALES

With appropriate hormone replacement therapy, female patients with HH can develop secondary sexual characteristics, maintain normal sex steroid concentrations, lead healthy sexual lives, and may also achieve fertility.[32] Several regimens of treatment with different administration routes exist. The choice of treatment depends on the therapeutic goal, the timing of treatment, and the personal preference of each patient.[3] It is important to know that randomized controlled trials of hormonal treatment in HH and data from clinical observational studies are limited. There is no uniform treatment regimen used internationally.

In girls, the therapeutic objectives are breast development, uterine growth, cornification of the vaginal mucosa, feminine appearance, and promotion of psychosexual development with respect to emotional life and sexuality. In addition, pubertal induction also increases uterine size, which is important for future pregnancy. Finally, optimizing linear growth to achieve an adult height close to the target height range is important, along with acquiring normal bone mineral density. Most therapeutic regimens inducing feminization in CHH are not evidence-based and usually arise from expert opinions. Many regimens have mirrored Turner syndrome treatment.[33]

Approaches to Treatment

Estrogen preparations

Both oral and transdermal estradiol induce feminization; however, the available protocols vary widely.[34] Transdermal estradiol administration is often started at low doses, sometime just with nocturnal applications, with the goal of mimicking estradiol levels during early puberty. The estradiol dose should then be increased gradually every 4 to 6 months.[35] After maximizing breast development and/or after breakthrough bleeding, cyclic progesterone therapy is added. Thus, cyclic progesterone may be implemented 12 to 24 months after initiation of estrogen treatment. In most females with HH, this therapy is effective to induce breast development, promote normal secondary sex characteristics, increase uterine size, accelerate linear growth, and induce withdrawal bleeding. However, this treatment does not restore ovulation. Hormonal treatment is required in adult females with HH to maintain bone health, improve emotional and sexual life, and promote general well-being.[33]

Treatment of functional hypothalamic amenorrhea (HA) involves nutritional rehabilitation as well as reductions in stress and exercise levels.[36] Many women with functional HA have an element of disordered eating or an incipient eating disorder that may require psychological support to facilitate a change in eating habits. In those with a formally diagnosed eating disorder, such as anorexia nervosa or bulimia nervosa, referral to a specialized eating disorder service is recommended to enable these patients to be appropriately treated by a multidisciplinary team, including psychiatrists. Improving the energy deficit often requires behavioral changes, and weight gain may need to be supervised by a registered dietitian or nutritionist. Reversing the negative energy balance by restoration of body weight or fat mass and/or reduction in exercise intensity may be sufficient to restore menses and improve rates of conception in some patients with functional HA. Some clinical trials have demonstrated the potential efficacy of leptin treatment in functional HA.[37] Hormone replacement therapy should be considered if this alone fails to restore menses and/there are ongoing skeletal or psychosocial concerns.

Fertility in women with congenital hypogonadotropic hypogonadism: Use of gonadotropins

Infertility in women with CHH is caused by impaired pituitary secretion of gonadotropins, leading to impaired ovarian stimulation and chronic anovulation. The combination of small ovaries, decreased antral follicle count, and low circulating anti-Müllerian hormone concentrations observed in women with CHH could suggest an alteration in ovarian reserve and a poor fertility prognosis. However, ovulation induction can still lead to a good fertility outcome.[38] Before considering ovulation induction, radiographic studies to evaluate both the integrity and the permeability of the uterine cavity and fallopian tubes should be completed. The goal of ovulation induction therapy in female patients with CHH is to obtain a mono-ovulation to avoid multiple pregnancies. Ovulation can be achieved either with pulsatile GnRH therapy or stimulation with gonadotropins: either extracted or rFSH treatment followed by hCG or human recombinant LH (rLH) to trigger ovulation.[39,40] The therapeutic choice will depend on the expertise of each center and the local availability of the different medical therapeutics.[38] Estradiol is necessary to maintain optimal cervical mucus production and endometrial thickness, which in turn are needed for sperm transit and embryo implantation. Typically, subcutaneous human menopausal gonadotropins (hMGs; FSH plus hCG) are sufficient to induce ovulation and the starting dose of hMG is often increased or decreased depending on the ovarian response as assessed by repeated serum estradiol measurements or by using ultrasonography to count and measure maturing follicles every other day.[41]

SUMMARY

HH refers to a broad group of disorders characterized by impaired neuroendocrine function resulting in delayed puberty. Because the identification of the GnRH receptor genetic variant associated with CHH, knowledge regarding inheritance patterns and specific genes has greatly expanded. The use of focused genetic panels has hastened the diagnostic process by facilitating molecular diagnosis. Nevertheless, the number of genes included on the test panels is limited, which means that "negative results" cannot exclude the diagnosis of CHH. Another caveat is that increasing numbers of "variants of unknown significance" are detected. Hence, distinguishing novel rare deleterious variants from benign variants may be problematic in some situations.

CLINICS CARE POINTS

- Delayed puberty is defined by the absence of breast development by age 13 years in girls or absence of testicular enlargement $\geq$ 4 mL by age 14 years in boys.
- Congenital hypogonadotropic hypogonadism is due to deficient production, secretion, or action of GnRH and is characterized by incomplete or absent puberty in the setting of low gonadotropin and sex steroid concentrations.
- In some cases, hypogonadotropic hypogonadism (HH) is detected early in life because of small phallic size and an absent mini-puberty of infancy. When it is certain that spontaneous puberty will not occur, the timing of pubertal induction should generally match the boy's peers or family history.
- The choice of HH treatment depends on the therapeutic goal, the timing of treatment, and the personal preference of each patient.

DISCLOSURE

The authors have nothing to disclose.

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