Hypogonadotropic Hypogonadism: A review

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Abstract
Male hypogonadotropic hypogonadism (HH) is failure of the testes to produce androgens and sperms secondary to congenital or acquired diseases affecting the hypothalamus and/or the pituitary gland. Hypogonadotrophic hypogonadism is suspected if the patient presents with Micropenis with or without cryptorchidism in infancy, delayed or absence of pubertal sexual maturation in adolescents (15-18 yrs age), primary infertility in adults and late onset hypogonadism in aging males. Diagnosis is confirmed by low serum follicle stimulating hormone levels, luteinizing hormone levels and testosterone levels. Imaging (MRI/CT) of brain should be done to rule out pituitary lesions. Treatment requires Androgen replacement therapy till/when fertility is not desired. For fertility Gonadotropins are started to stimulate spermatogenesis. HH is one of the rare conditions in which specific medical treatment can reverse infertility.

Keywords: Hypogonadotropic hypogonadism, Secondary hypogonadism, Male infertility, Subfertility, Azoospermia.

Introduction
Hypogonadism results from impaired testicular function affecting spermatogenesis and/or testosterone synthesis. The hypothalamus, Pituitary and the testes function in a coordinated manner to secrete Testosterone and maintain normal spermatogenesis. Hypothalamus secretes Gonadotropin releasing hormone stimulating the Pituitary gland to release Gonadotrophinsi.e. Leutinising hormoine(LH) and Follicle stimulating hormone (FSH).[1,2] These hormones act on androgen and sertoli cell receptors on Leydig cell sand Sertoli cells of testes respectively to release Testosterone and Inhibin B supporting spermatogenesis.[3,4] Hypothalamic Pituitary dysfunction results in secondary testicular failure also known as Hypogonadotropic hypogonadism (HH) in contrast to primary testicular failure which is also called Hypergonadotropic hypogonadism. HH, secretion of gonadotropin releasing hormone (GnRH) is absent or inadequate. Isolated lack of production or inadequate biosynthesis of pituitary gonadotropins may also result in HH.[5] The prevalence of this form of hypogonadism has been estimated to range from 1:10,000 to 1:86,000 individuals.[6]

Aetiology
Hypogonadotrophic hypogonadism (HH) can be congenital (CHH) or acquired. Congenital causes include Anosmic i.e. Kallman's syndrome and Normosmic i.e. Idiopathic HH. (IHH). Genetic factors causing a deficit of gonadotropins may act at the hypothalamic or pituitary level. Mutations in KAL1, FGFR1, and GNRHR genes are the most common and account for 15 to 20% of all cases of IHH. Mutations in GPR54, LEP, LEPR, HESX1, NROB1, PROP1, LHX3, FSHB, and LHB genes account for less than 5% of cases of IHH.[7] These should be screened for prior to assisted reproduction. Kallman's syndrome is a X linked disorder due to mutation of KAL-1 gene which encodes for neuronal cell adhesion. This results in inability of the GnRH secreting cells to migrate from the olfactory placode to the olfactory bulb and hypothalamus. IHH is characterized by low levels of gonadotropins without anatomical or functional abnormalities. One Indian study reported, mutations in the AR gene are less likely to cause azoospermia and oligozoospermia.[8]

Acquired causes include pituitary tumors, craniopharyngioma, head injury, drugs like sex steroids, GnRH analogues, opiates, marijuana, infiltrative diseases, hyperprolactinemia, brain radiation, exhausting exercise, abusive alcohol intake and systemic disease like hemochromatosis, sarcoidosis and Histiocytosis.(Table 1)

Diagnosis
From a diagnostic perspective, minipuberty offers a unique window of opportunity for the early diagnosis of CHH. Micropenis and cryptorchidism raise a suspicion of CHH in male infants, as these signs may reflect the lack of activation of the HPG axis during fetal and postnatal life but currently the importance of evaluating minipuberty is not known. The advance of biochemical testing with minimal blood samples (e.g., blood dry spots) offers the potential to assess the HPG axis function in neonates in normal and disease states. In such cases, hormone testing at 4 to 12 weeks of life may be used to assist in the diagnosis.[9] On the basis of current evidence, early intervention to mimic the gonadotropic surge in the first 6 months of life is not indicated.[10]

In adolescence, clinical features include delayed or absent puberty. Delayed puberty is classically defined as absence of testicular enlargement (volume <4 ml) in boys by the age of 14 years.[11,] Other features include normal adrenarche (pubic hair), eunuchoidal body proportion (arm span 2 cm >height), normal stature and growth in childhood, congenital anomalies like anosmia, unilateral renal agenesis, cleft lip, colour blindness, hearing loss, Microphallus and cryptorchidism. Some genetic disorders like PraderWilli syndrome, Laurence Moon Biedl syndrome and Moebius syndrome are also related to this group. The clinical characteristics of HH and CDGP (constitutional delayed

growth and puberty) may be difficult to differentiate, as low gonadotropin and testosterone levels are found in both conditions.[9] The presence of micropenis and/or cryptorchidism argues firmly in favour of CHH, as these features are rarely seen in CDGP. Associated congenital phenotypes are also very useful as they indicate a syndromic form of CHH.[12] A definitive HH diagnosis must be confirmed only after the patient is 18 years of age.[1,17]

The appearance of clinical characteristics depends on when HH begins. Men presenting with HH that started in the prepubertal phase and was triggered by the intrinsic second GnRH peak exhibit eunuchoid body proportions, a delay in the development of secondary sexual characteristics, a high pitched voice, pre-pubertal testicles, and delayed bone maturation. Men with an initially delayed HH condition present with diminished libido, considerable weight gain, sexual impotence, hot flashes, and infertility. Infertility is one of the most frequent complaints among these patients and has a negative effect on their quality of life.[3,6] (Table 2).

HH may also be a component in Late onset hypogonadism presenting in aging men with varied symptoms.(Table 3)

Table 1: Etiology of Hypogonadotropic hypogonadism

Congenital	Idiopathic hypogonadotropic hypogonadism Normosmic Hyposmic/anosmic (Kallmann syndrome)
Acquired	Diencephalon (craniopharyngioma or meningioma) Hypothalamus or pituitary Empty sella syndrome Granulomatous illnesses Fractures of the skull base Ischaemic or haemorrhagic lesions in hypothalamic area Hyperprolactinaemia Drugs/anabolic steroids, radiotherapy Target organ resistance to androgens Testicular feminisation Reifenstein syndrome

Table 2: Signs and symptoms of pre- and post-pubertal hypogonadism.[3]

Pre-pubertal hypogonadism	Post-pubertal hypogonadism
Eunuchoidal stature	Normal stature
Small testes (usually, 6cm3)	Testes volume normal to slightly low (.10cm3); soft
Small penis (5cm)	Penis normal size
Lack of normal scrotal rugae and pigmentation	Normal scrotal rugae and pigmentation
Small prostate	Normal prostate
Scant facial, axillary and pubic hair	Thinning of facial, axillary and pubic hair
High pitched voice	Normal voice
Gynecomastia	Gynecomastia
Infertility	Infertility
Lack of libido	Loss of libido
Low bone mineral density	Low bone mineral density
Low muscle mass, high percentage of body fat	Low muscle mass, high percentage of body fat
Mild anemia	Mild anemia, Hot flashes, lack of male pattern baldness, decreased sense of well-being, Erectile dysfunction

Table 3: Symptoms typically met in late-onset hypogonadism (LOH)

• Diminished sexual desire and arousability (libido)
• Loss of erectile quality and frequency
• Loss of particularly nocturnal erections
• Depression, fatigue, lack of vigor, irritability
• Decreased intellectual activity: cognitive functions, spatial orientation
• Sleep disturbances
• Decrease in lean body mass, diminution of muscle volume, and strength
• Increase in visceral fat
• Decrease in body hair and skin alterations
• Osteopenia, osteoporosis, and increased risk of bone fractures

Investigations

Hypogonadism is substantiated by low Serum Testosterone level. In case of borderline values, based on levels of total testosterone, albumin and SHBG, free and bioavailable testosterone can be calculated. Due to diurnal variation, blood samples for testosterone assessment should be taken before 10.00 am to account for the circadian rhythm of male hormones. When low testosterone levels are found, the gonadotropin (FSHand LH) levels must be analyzed. A low pituitary hormone level confirms the HH diagnosis.[3,5]

A prolonged stimulated intravenous GnRH test (100 mcg followed by 500 mcg) can be useful to differentiate hypothalamic and Pituitary causes. In hypothalamic GnRH deficiency, LH and FSH gradually appear, whereas hypo responsiveness occurs in the pituitary cases.[5] A suspected tumour (pituitary, prolactinoma and craniopharyngioma) requires imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] of the sella region & olfactory bulb(Kallman's syndrome) and a complete endocrine work-up including thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1) and cortisol had to be measured to exclude multiple defects. In addition, ferritin or transferrin saturation and angiotensin converting enzyme are measured to exclude haemochromatosis and sarcoidosis respectively.[10]

A hand X-ray will determine the bone age and dual energy X-ray absorptiometry scan can assess BMD. Genotyping for known monogenic causes of HH is at present a research procedure, but may be warranted where there is a positive family history. If performed, it had to be accompanied by genetic counselling.[10]

Management

Normal androgen levels and subsequent development of secondary sex characteristics (in cases of onset of hypogonadism before puberty) and a eugonadal state can be achieved by androgen replacement alone. However, stimulation of sperm production requires treatment with human chorionic gonadotropin (hCG) combined with recombinant FSH, urinary highly purified FSH or human menopausal gonadotropins (HMGs).Various gonadotropins, either urinary or recombinant, are presently available. The urinary gonadotropin forms are produced from the urine of menopausal women and include human menopause gonadotropin (hMG), which contains urinary FSH and LH. Another commonly used urinary gonadotropin is highly purified urinary FSH.[3,4,6] Impregnation rates can reach 50 to 80% with a sperm concentration of 5 million per mL.[4,5] The predictors of treatment success are described as an increased baseline testicular volume, no history of cryptorchidism, a history of sexual maturation, and no previous testosterone replacement therapy [5] although these patients may need two years of hormonal therapy before spermatogenesis is triggered.[4,5] Because a long period is necessary to restore spermatogenesis, it is advised that every man who aims to become a father start treatment 6 to 12 months before attempting to conceive.[4,5] Gonadotropic treatment starts with the administration of 1,000 to 2,500 international units (IU) of isolated hCG twice a week for 8 to 12 weeks. This initial phase is the induction phase, which is crucial for allowing testosterone levels to increase. In certain cases, hCG alone can induce spermatogenesis. In individuals who do not have sufficient endogenous FSH, treatment can continue with the coadministration of 75 to 150 IU hMG three times per week for up to 18 months, as the presence of FSH is crucial for stimulating spermatogenesis. Recombinant FSH can be used in place of hMG, with patients receiving 150 IU three times per week for the same period of time. This combined treatment provides considerable testicular growth in most patients, in addition to spermatogenesis in up to 90% of patients.[4,5]

If hypogonadotropic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is pulsatile GnRH. In patients who have developed hypogonadism before puberty and have not been treated with gonadotropins or GnRH, one to two years of therapy may be needed to achieve sperm production.

Generally, androgen replacement should not be given to men who are considering parenthood or in case of male infertility as Testosterone suppresses pituitary production of LH and FSH. Therefore Hypogonadal men wanting to preserve their fertility and at the same time benefiting from TRT effects can be prescribed Selective Estrogen Receptor Modulators(SERMs) or testosterone plus low-dose hCG.[13] In obese men, low levels of testosterone may exist due to the conversion of testosterone to oestradiol by the enzyme aromatase. Anti-oestrogens and aromatase inhibitors may help in these patients elevating FSH and LH and potentially increase sperm quality, next to weight reduction.

About 10% of idiopathic HH have been shown to achieve sustained reversal of hypogonadism after treatment discontinuation.[14]

Spontaneous conception can be achieved within 6-9 months after beginning gonadotropin treatment but can require up to two years.[15]However, the effectiveness is around 70%.[16] About 30% male CHH patients had no or few sperm with conventional therapy (i.e. azoospermia, oligospermia. Therefore, if a spontaneous pregnancy does not occur after 20 months assisted reproductive technologies may be considered to achieve pregnancy. [17]For this specific population, the overall pregnancy rate per ET cycle was about 46%. Fertilization, implantation and live birth rates (72, 36 and 40%) showed no significant differences as compared to infertility due to other causes.[18]

Intrauterine insemination (IUI) is a good option for men, who have achieved good spermatogenesis (a sperm concentration higher than 5- 6x106/mL) with hormone therapy but failed to impregnate their partner. In these cases, hysterosalpingography should be performed on the partner to confirm tubal patency. Intracytoplasmic sperm injection (ICSI) is the treatment of choice for patients who have completed at least one year of therapy and exhibit sperm concentrations of < 5mill/ml.

It is common to, find concomitant female infertility in these cases.[17] Bakircioglu et al. evaluated 22 ICSI attempts with a pregnancy rate of 54.5% [17] Zorn et al. reported four men with HH who underwent 10 ICSI cycles after hormone

treatment. This group achieved a 67% fertilization rate and a 30% pregnancy rate per cycle.[19] Until recently, remaining childless, adoption or sperm donation were the only options for HH patients with persistent azoospermia despite long periods of hormone therapy. For these patients, testicular sperm extraction (TESE) could be an excellent option to achieve a pregnancy. [20] Some authors have published results with TESE in azoospermic men with HH; for example, Fahmy et al. used TESE to successfully recover spermatozoa in 11 out of 15 patients (73%) and, more recently, Akarsu et al. found sufficient spermatozoa for ICSI and cryopreservation for future cycles in all cases.[20,21]

Conclusions

Male hypogonadotropic hypogonadism may be congenital or acquired due to lesions of hypothalamus and /or Pituitary gland. Diagnosis is confirmed by low gonadotropins and testosterone levels. Clinical features depend on the age of presentation. Fertility is induced by hCG and FSH preparations or pulsatile GnRH. Life long Testosterone replacement therapy (TRT) may be required in majority. 10 % of cases may have a reversible phenotype, and this may enable earlier withdrawal of therapy.

Source of Funding

None.

Conflict of Interest

None.

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