

Normosmic Idiopathic Hypogonadotropic Hypogonadism: A Case Report

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Background. Idiopathic hypogonadotropic hypogonadism (IHH) is manifested as absent or incomplete puberty and biochemically low levels of sex hormones, with low or inappropriately normal gonadotropin hormones. In the absence of structural or functional lesions of the hypothalamic or pituitary gland, the hypogonadism is referred as idiopathic hypogonadotropic hypogonadism (IHH). IHH is a genetically heterogeneous disorder which can be caused by pathogenic variants affecting proteins involved in the pulsatile gonadotropin-releasing hormone release, action, or both.

Case Presentation. A 16-year-old male who presented to the endocrinology clinic with complaints of micropenis and absent secondary sex characteristics. Work up showed an unremarkable cranial MRI, low testosterone, LH, normal FSH, with normal Karyotyping.

Conclusion. Idiopathic hypogonadotropic hypogonadism (IHH) is a rare genetic disease with a complex and still have more to discover about its pathogenesis. The requirements for the diagnosis include low testosterone, low or normal serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations, and a normal appearance of the hypothalamus and pituitary region on magnetic resonance imaging (MRI). A prompt recognition of a clinical hypogonadotropic hypogonadism is pivotal especially in a peripubertal age to initiate early sex hormone replacement as the failure of secondary sex characteristics could have a derogatory impact on individual's personal and social life.

Keywords. Hypogonadism, Idiopathic hypogonadotropic hypogonadism (IHH)

Introduction

Idiopathic hypogonadotropic hypogonadism is a rare disease with a complex and still largely unknown pathogenesis that is characterized by delayed/absent puberty and/or infertility due to an insufficient stimulation of an otherwise normal pituitary-gonadal axis by gonadotrophin-releasing hormone (GnRH) action. Biochemically it is characterized by low levels of sex steroids (testosterone or estradiol) in the presence of lower normal levels of gonadotropins (LH and FSH).

It is a rare disease with an incidence of 1-10 in 100,000 live births with a variable mode of inheritance, affecting 1:8000 males and 1:40 000 females. (1)

It can be associated with either a normal or defective sense of smell, referred as normo-osmic ICH (nICH) or Kallmann syndrome (KS), respectively. Males frequently present with defective androgenisation and growth at a peripubertal age.

Case Presentation

A 16-year-old male presented to the endocrinology clinic with complaint of micropenis. He is currently a Junior high school student, ranked 5th of his class with no developmental milestone delays noted. He has poor physical performance described as diminished strength and easy fatigability on doing strenuous activities such as sports. He had no history of anosmia, problems with visions, and headache. He has unremarkable family history.

On physical examination, he was ambulatory with stable vital signs. He presented with eunuchoid proportion (Figure 1) with a height of 158 cm and arm span of 157 cm, with distance from the symphysis pubis to the floor exceeds the distance from the crown of the head to symphysis pubis more than 5 cm measuring 89 cm and 71.5 cm respectively. There were absent facial, axillary and pubic hairs, bilateral gynecomastia (Figure 2), and penile length of 3 cm with hypopigmented scrotum and small testes (Figure 3). The rest of physical examination were unremarkable.

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Laboratory workup done to patient showed a hypogonadotropic hypogonadism with low testosterone, low LH, normal FSH, normal TSH and Prolactin. Cranial MRI showed unremarkable findings. Chromosome analysis was done revealing a karyotype with no numerical and structural aberrations and an XY sex chromosome complement in all 50 cells examined.

Testosterone replacement therapy with injectable long-acting T undecanoate was offered to patient at 750 mg IM followed by 750mg at 4th week, and 750 mg every 10 week, and currently undergoing the treatment.



Figure 1



Figure 2



Figure 3



Figure 4



Figure 5

Discussion

Idiopathic hypogonadotropic hypogonadism (IHH) is a family of genetic disorders that are associated with defects in the production and/or action of hypothalamic peptide that controls human reproduction, the so-called GnRH. The lack of endogenous hypothalamic gonadotropin-releasing hormone (GnRH) secretion/action in patients with IHH cannot be proven by direct assay of GnRH in the portal circulation (5). IHH can occur either with normal olfaction (normosmic IHH) or with anosmia (Kallman syndrome).

Hypogonadotropic hypogonadism is characterised by low levels of testosterone or oestradiol in the presence of impaired or defective secretion of luteinizing (LH) and follicle stimulating hormone (FSH) from the pituitary gland. In the absence of any anatomical or functional lesions of the pituitary or hypothalamic gland, the hypogonadotropic hypogonadism is referred to as idiopathic hypogonadotropic hypogonadism (IHH) (2).

Idiopathic hypogonadotropic hypogonadism with normal sense of smell (normosmic IHH) or with hyposmia or anosmia (Kallman syndrome) is a complex and rare disorder characterized by insufficient GNRH neuronal action on an otherwise normal hypothalamo-pituitary- gonadal axis. This could be due to defective development or migration of GNRH neurones, impaired secretion of GNRH from neurones, disrupted interaction between the GNRH ligand and its receptor, or impaired secretion of LH and FSH (1). To date, pathogenic variants in around 50 genes have been reported to cause IHH

which account for up to 50% of IHH cases, suggesting that further genes remain to be discovered (4). Several genes have been implicated in the etiology of IHH. Genes that typically cause the normosmic forms of IHH include mutations in *KISS1R* (kisspeptin 1 receptor gene, formerly *GPR54*, located on chromosome 19p13.3 and encodes the G-protein coupled receptor-54), loss-of-function mutations in the GnRH receptor gene (*GNRHR*), Mutations of *GNRH1* (GnRH 1 gene), the gene encoding preproGnRH, mutations in *TAC3* and *TACR3* (tachykinin 3 and tachykinin 3 receptor genes, encoding neurokinin B and its receptor, respectively). (5)

The diagnosis of IHH requires the following findings; low testosterone, inappropriately low or normal serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations rather than the high concentrations expected with primary gonadal failure, otherwise normal anterior pituitary function, normal appearance of the hypothalamus and pituitary region on magnetic resonance imaging (MRI) (5).

The choice of therapy for IHH depends upon the patient's age and desire to achieve one or more of the following goals: Induction of puberty and/or maintenance of sexual maturation, and induction or restoration of fertility.

Conclusion

Idiopathic hypogonadotropic hypogonadism (IHH) is a rare genetic disease with a complex and still have more to discover about its pathogenesis. The requirements for the diagnosis include low testosterone, low or normal serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations, and a normal appearance of the hypothalamus and pituitary region on magnetic resonance imaging (MRI). A prompt recognition of a clinical hypogonadotropic hypogonadism is pivotal especially in a peripubertal age to initiate early sex hormone replacement as the failure of secondary sex characteristics could have a derogatory impact on individual's personal and social life.

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