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Congenital Idiopathic Hypogonadotropic Hypogonadism: A Case Report

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Abstract

Congenital idiopathic hypogonadotropic hypogonadism (IHH) is caused by the lack of production or physiological response to gonadotropin releasing hormone (GnRH). A wide variety of genetic mutations have been implicated in the disorder demonstrating autosomal dominant, recessive and X-linked inheritance patterns. Diagnosis of IHH is complicated by its similarity in presentation to a constitutional delay of puberty (CDP) and often goes undiagnosed in patients under the age of 18. Once IHH is identified, the effects of the disturbed HPA axis must be addressed. In this report, we offer a brief overview of the diagnosis and management of IHH and present the case of a 27 year old male with undiagnosed IHH.

Keywords: Hypogonadotropic hypogonadism; Microphallus; Kallmann syndrome

Case Report

A 27 year old white male presented to a family medicine clinic with complaint of a changing skin lesion that was a melanoma in situ. As a result, he had a full-skin exam and was found to have a microphallus, undescended testes, and minimal pubic hair distribution. He had a normal sense of smell. Laboratory evaluation showed total testosterone to be 26 ng/dL (250-1100 normal), LH 0.4 mIU/mL (1.5-9.3 normal), and FSH 1.6 mIU/mL (1.6-8.0 normal). Prolactin, PTH, and calcium were within normal limits, as well as his CBC and BMP. MRI of the brain showed no lesions of the hypothalamus or pituitary gland. An abdominal CT and DEXA scan revealed undescended testes and osteopenia, respectively. He was diagnosed as IHH. The patient was provided with supplementary vitamin D, calcium and referrals to endocrinology and urology for orchiopexy. This patient was followed at my clinic regularly. By the time that this manuscript was written, urologist evaluated the patient and orchiopexy was scheduled.

Background

Congenital Idiopathic Hypogonadotropic Hypogonadism (IHH) is a condition caused by the deficiency of or insensitivity to gonadotropin releasing hormone (GnRH) with an estimated prevalence of 1:10,000 [1]. Persons with this disorder are predominantly male, with a male-to-female of 5:1. Signs and symptoms of IHH are directly related to sexual development and age-related reproductive activity such as microphallus, low testicular volume, cryptorchidism, failure to undergo sexual maturation, low libido, and infertility [2]. Males exhibit a lack of muscular development and failure of the voice to deepen, whereas females typically exhibit minimal to a complete lack of breast development coupled with primary amenorrhea. Both sexes generally have some pubic hair due to hormones of adrenal origin and a eunuchoidal appearance due to the delayed closure of the epiphyseal plates [3]. Anosmia is a distinguishing characteristic of Kallmann syndrome from other subtypes of IHH. The choice for particular hormone replacement therapy protocol aimed at virilizing the patient will depend on age at diagnosis and local practices [4]. In general, treatment options most require lifelong treatment but for the rare cases of reversal [5].

Discussion

Identified causes for IHH are genetic in nature and come from a variety of mutations affecting genes involved hypothalamic-pituitary-gonadal axis. Phenotypic expression of these genes may be inherited in an autosomal dominant, recessive or X-linked pattern [3] while numerous involved loci have been identified. In addition to recessive, autosomal dominant and X-linked forms oligogenicity is a significant contributor. Certain clinical features in men and women are highly associated with genetic causes KS. Synkinesia (KAL1), dental agenesis (FGF8IFGFR1), digital bony abnormalities (FGF8IFGFR1) and hearing loss (CHD7) can be useful for prioritizing genetic screen [6].

Although we presented a case of IHH, it is not unusual for congenital causes of hypogonadotropic hypogonadism, such as Kallmann syndrome to be diagnosed in young adult. Gonadotropin-releasing hormone (GnRH) deficiency in human presents either as normosmic idiopathic hypogonadotropic hypogonadism (nIHH) or with anosmia (Kallmann syndrome) [7].

Research data indicates Prokineticin 2, a protein, plays a critical role in the pathway of olfactory bulb development and GnRH secretion. It works through both a G protein-coupled receptor and an intracellular calcium-signaling pathway. Homozygous loss-of function mutation in the PROK2 gene cause IHH and Kallmann syndrome [8].

Clinical evaluation for patients with normosmic IHH is challenging since symptoms are often consistent with constitutionally delayed puberty (CDP). Identifying undescended testis is a clinical clue that the child has IHH. Establishing the diagnosis requires correlation of the history and physical with laboratory tests [9,10]. When IHH is suspected, evaluation includes demonstrating low concentrations of sex steroid hormones, inappropriately low or normal LH and FSH levels, with otherwise normal pituitary function aside from GnRH-related hormonal disturbance. Imaging of the hypothalamus and pituitary is necessary to rule out structural abnormalities that could cause similar hormonal changes [11].

Diagnosis of IHH is further complicated by the social stigma surrounding sexual disorders; leaving symptoms in some patients go unreported. These symptoms, such as micropenis in this case, can be useful in differentiating IHH and CDP. Therefore, a genitourinary

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exam can be beneficial when either of these conditions is suspected, as treatment may vary. Micropenis and cryptorchidism are both conditions of IHH that require early treatment, before the age at which CDP can be ruled out [12,13].

The effects of GnRH deficiency extend beyond infertility and lack of secondary sex characteristics. Studies have demonstrated hypogonadotrophism to have effects on muscle development and physical strength, mood, and bone development [14].

Osteoporosis is a common result of hypogonadism. Osteoporosis in men has been shown to increase both morbidity and mortality. Several therapies including bisphosphonates, and androgen supplementation have been shown to be effective treatment for males [15].

Cryptorchidism is associated with an increased risk of testicular cancers. This risk nearly doubles when cryptorchidism is bilateral. Orchiopexy will reduce, but not eliminate the risk for cancer. Timely diagnosis is critical as age at which orchiopexy is performed has been shown to determine cancer risk reduction [12].

Conclusion

The diagnosis of IHH in this patient is important for his future health. Osteoporosis, increased risk of testicular cancer secondary to cryptorchidism, sexual dysfunction, and infertility are just a few of the sequelae associated with IHH. When diagnosed early, these co morbidities can be reduced or even eliminated. This case highlights the value of obtaining a detailed history and performing a thorough physical examination as this patient's risk of cancer, fractures, and infertility could have been dramatically reduced with an earlier diagnosis. This case also indicated the importance of collaboratation between primary care physician and specialty physicians.

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