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Hypogonadotropic-hypogonadism (Kallman Syndrome) in Young Adult

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Abstract

Background: Kallmann syndrome (KS) is a rare disorder first described in 1856 and later studied by Kallmann in 1944⁽¹⁾. It is now designated as olfactogenital dysplasia with an association between agenesis of the olfactory bulbs and hypogonadism. The prevalence of KS is still unknown. The reported incidence is 1 in 8000 to 1 in 10 000 in men and rare in women⁽²⁾. More than 24 genes are underlying KS that have been identified⁽³⁾. Mutations in these genes are thought to interfere with the expression of cell markers that guide migrating neurons, leading to failed migration of GnRH neurons and olfactory neurons to the forebrain during fetal development. The main clinical characteristics of KS include hypogonadotropic hypogonadism and anosmia or hyposmia. Less common phenotypes include cardiovascular anomalies, unilateral renal agenesis, cleft palate and cleft lip, cryptorchidism and osteoporosis⁽⁴⁾. Magnetic resonance imaging (MRI) can show abnormalities of the olfactory system and other forebrain structures⁽⁵⁾. Other exceptions may be discovered using MRI because of its high resolution and multiplanar capabilities, such as pituitary abnormalities⁽⁶⁾.

Key words: Hypogonadotropic-hypogonadism, Kallmann syndrome, olfactogenital dysplasia.

Case Presentation

An 18-year-old male patient presented to our hospital with complaints of childish voice. He was born to a nonconsanguineous marriage, full-term normal vaginal delivery. He has three siblings, and all are healthy. At birth, micropenis was observed but took no further action. He went circumcision at the age of one year. His development was apt and passed in schools with flying colours. In high school, he was bullied by his classmates for his voice. He also noted decreased ability to smell and absent morning erections. He has no history of vision difficulty, difficulty in hearing, seizures and movement disorders. No significant family history from both parental sides.

On examination, his height was 160cm, weight of 55kg, arm span of 165cm with the upper segment to lower segment ratio of 1.1:1. He has a high pitch voice. He has no moustache, beard, absent hair over the axilla and pubic region. He has bilaterally descended testes with a pre-pubertal size of around 1 cm and a penile length of 1.8cm. On general examination, he has pallor. His systemic examination was remarkable for the reduced smell.



Photographs showing before treatment and after testosterone therapy

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A complete haemogram was significant for anaemia (Hb- 11.5gm/dl). His serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone revealed hypogonadotropic hypogonadism and tabulated below.

Hormones	Patient values	Reference range
Serum FSH	0.33 mIU/ml	1–10.5 mIU/ml
Serum LH	0.13 mIU/ml	1.9–9.4 mIU/ml
Serum testosterone	100ng/Dl	

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

On Imaging , Ultrasound abdomen revealed the normal study. Scrotal ultrasound showed bilateral small testis size and volume (2ml). MRI brain showed hypoplastic olfactory bulbs.

The patient was started on parenteral testosterone supplements to improve his secondary sexual characters. The patient was being followed up regularly every three months. Follow up demonstrated improvement in anaemia, voice, phallic size, and development of sexual characters.

Discussion

KS is an isolated form of hypogonadotropic hypogonadism in combination with a defect in the sense of smell. Due to flaws in olfactory structures (bulbs, grooves, tracts) and altered GnRH-secreting neurons' migration into the preoptic and hypothalamic regions⁷. It is a genetically heterogeneous disease inherited in an X-linked, autosomal dominant or autosomal recessive pattern. The most prevalent is an X-linked form that charts to the KAL1 gene, which encodes for a neuron adhesion molecule believed to be accountable for guiding the migration of LH-releasing hormone-secreting neurons to the medial basal hypothalamus.

Our outpatient manifested with delayed puberty, characterized by high pitched voice, absence

of facial and axillary hair and sparse pubic hair, micropenis and bilateral small testes. The hormonal evaluation showed low FSH, low LH and low testosterone levels. A diverse group of disorders with varied pathophysiology comprise hypogonadotropic hypogonadism or hypothalamic-pituitary hypogonadism. Examples include an isolated abnormality in hypothalamic GnRH, isolated abnormality in pituitary gonadotropins (LH, FSH) and conditions in which both hypothalamic and pituitary dysfunction is present. The differential diagnosis will include KS, GnRH receptor mutation, GPR54 mutation, DAX-1 mutation and hypopituitarism⁸.

In this case, the diagnosis of KS is straightforward because of the hypogonadotropic hypogonadism in association with hyposmia and documented radiologic findings in MRI.

Morphological anomalies of the olfactory apparatus in KS are best evaluated with MRI. Cranial MRI, in our case, revealed a hypoplastic bilateral olfactory bulb. The pituitary gland is normal.

Clinical diagnosis of KS in adults is reasonably apparent, depending on the co-existence of anosmia with subnormal levels of gonadal steroid and gonadotropins. However, the diagnosis may be difficult to establish in pre-pubertal age patients who may require genetic testing and MRI⁹. In these patients, MRI will aid in the diagnosis of KS by demonstrating characteristic abnormalities in olfactory sulci and tracts. To diagnose KS, infiltrative disorders and space-occupying lesions of the pituitary must be excluded. Novel researches have revealed ethmoid bone anomalies and pituitary aberrations on computed tomography in KS patients.

Therapeutic objects in the adolescent male with CHH are well defined: to produce virilization, to reach optimal adult height, to acquire average bone mass and body composition, to achieve normal psychosocial development, and to gain fertility. Gonadotropins are used for fertility treatments in

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adult patients with CHH and can also stimulate pubertal maturation in adolescent males with CHH. An additional advantage of gonadotropin treatment compared with T treatment is the stimulation of testicular growth and spermatogenesis. Therefore, gonadotropin therapy may contribute to crucial psychological reassurance in teenagers and heighten self-confidence¹⁰.

In summary, we have a KS case who presented with a micropenis early in life but unfortunately was not further evaluated. He subsequently presented with eunuchoid body proportion, high pitched voice, absence of facial and axillary hair and sparse pubic hair, micropenis and bilaterally descended prepubertal testes. Associated findings were hyposmia and facial anomalies, namely congenital absence of puncta and smooth philtrum. The hormonal evaluation was consistent with hypogonadotropic hypogonadism. Cranial MRI showed aplastic right olfactory bulb and hypoplastic left olfactory bulb.

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