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Kallmann Syndrome: A Case Report

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ABSTRACT

Kallmann syndrome (KS) is a rare genetic disorder characterized by hypogonadotropic hypogonadism associated with altered sense of smell. KS is due to failure of intrauterine migration of olfactory axons and gonadotropin releasing hormone (GnRH) neurons from olfactory plate to the hypothalamus. There is defective hypothalamic gonadotropin releasing hormone (GnRH) synthesis and agenesis or hypoplasia of olfactory bulbs and olfactory sulcus. The prevalence is estimated at one in 10,000 males and one in 50,000 females. We described a case of 22 years male patient who presented with delayed puberty, characterized by absence of facial and axillary hair and sparse pubic hair, micropenis and bilateral small testes and associated with decrease smelling capacity. Diagnostic evaluation consist of hormonal evaluation which revealed revealed low levels of testosterone, LH & FSH with normal levels of TSH, prolactine and cortisol. MRI shows agenesis of olfactory bulbs and grooves, absence of the olfactory sulcus resulting in fused gyrus rectus and medial orbital gyrus forming a single gyrus. Furthermore, this patient had partial empty sella, which is one of the anomalies that are associated to this syndrome. It is planned to manage this case with Hormonal replacement therapy to induce puberty and later on pulsatile GnRH will be administered when fertility will be desired.

Keywords: Kallmann syndrome, Hyposmia, Anosmia, Hypogonadotropic hypogonadism, Magnetic Resonance Imaging.

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INTRODUCTION

Kallmann syndrome is an inherited disorder characterized by hypogonadotrophic hypogonadism^[1]. KS results from defective hypothalamic gonadotropin releasing hormone (GnRH) synthesis, and is associated with anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia^[2]. There are alterations of several specific genes that prevent the migration of the gonadotropin-releasing hormone (GnRH) neuronal cells and the olfactory nerve from their common origin in the olfactory placode early in fetal development^[3]. It is a rare genetic disorder with a prevalence of one in 10,000 males and one in 50,000 females^[4]. Cryptorchidism, gynecomastia are seen in most of the patients with micropenis occurring in approximately 50% of affected males^[4]. The primary hormonal defect is a failure of GnRH secretion by the hypothalamus, leading to secondary testicular failure^[5].

Case report:

A 22 year old man presented to department of endocrinology at Gauhati Medical College, Assam, India, with a history of small sized penis since birth with poor development of other secondary sexual characteristics and decreased smelling capacity. He had delayed growth spurt noticed at 15 years of age. He was born to non- consanguineously married couple with no significant antenatal and natal history. On local examination of genitalia we found sparse pubic hair, small penis and bilateral small testis. On blood examination, we found low level of testosterone (1.52 ng/dl), low LH (0.53 mIU/ml) & low FSH (1.3 mIU/ml) and normal TSH (2.5 mIU/ml), PRL (7.9 ng/ml) and cortisol (10 mcg/dl at 8 AM) level. On MRI examination we found absence of bilateral olfactory bulbs and grooves (figure 2A). There is also absence of the olfactory sulcus resulting in fused gyrus rectus and medial orbital gyrus (figure 2B). There is associated partial empty sella with height of the anterior lobe measures 2.6 mm (figure 3).

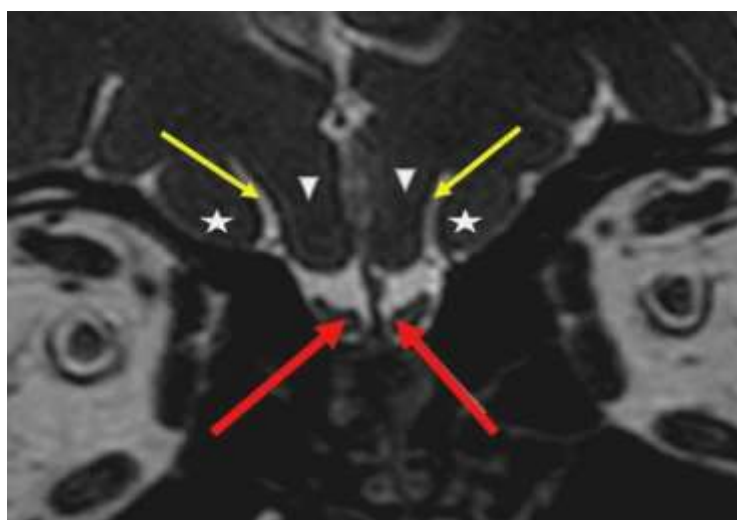


Figure 1: Normal olfactory bulbs & olfactory sulcus: Coronal T2WI image of a normal patient showing normal olfactory bulbs (red arrows), olfactory sulcus (yellow arrows) and gyrus rectus (arrow heads) & medial orbital gyrus (stars).

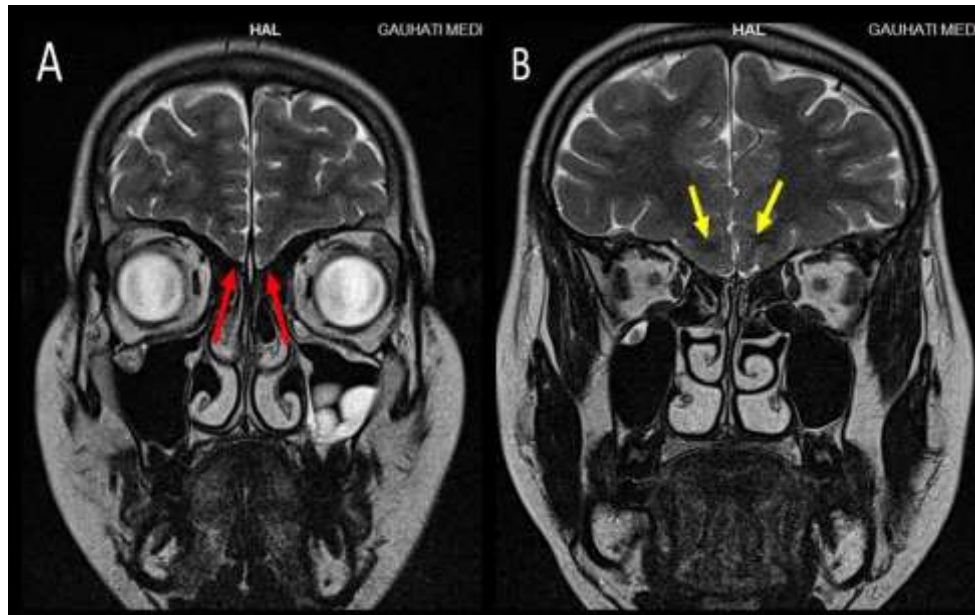


Figure 2: Kallmann syndrome: Coronal T2 weighted image through anterior orbital plane (2 A) and posterior orbital plane (2B) shows absence of the olfactory bulbs (red arrows) and olfactory sulcus (yellow arrows).

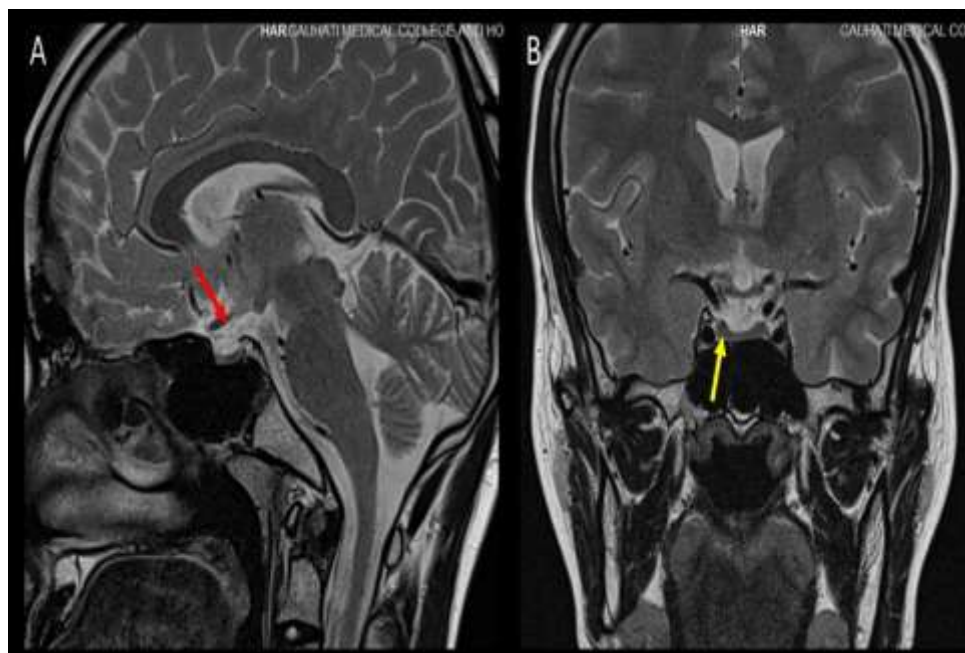


Figure 3: Partial empty sella: T2 weighted sagittal (A) & coronal (B) image of the patient shows partial empty sella (red arrow) which is compressing anterior pituitary gland (yellow arrow).

DISCUSSION:

Maestre de San Juan, a Spanish anatomist was described first in 1856, the association of hypogonadotropic hypogonadism and anosmia/hyposmia [6]. In 1944 by an American medical geneticist, Franz Josef Kallmann described a syndrome of primary eunuchoidism secondary to hypogonadotropic hypogonadism associated with congenital anosmia and therefore established that this syndrome can be hereditary [1]. It is a genetically heterogeneous disorder

and three modes of inheritance have been reported: X-linked recessive, autosomal dominant and autosomal recessive. The most prevalent is an X-linked form that maps to the KAL1 gene which encodes for a neuron adhesion molecule thought to be responsible for guiding migration of LH-releasing hormones-secreting neurons to the medial basal hypothalamus. Mutations in the KAL1 (Xp 22.3) gene are detected in 14% of familial cases and in 11% of sporadic cases [7]. Pathophysiology of Kallmann syndrome occurs due to failure of the embryonic migration of neuroendocrine GnRH neuronal cells from olfactory plate to the hypothalamus which causes defective hypothalamic gonadotropin releasing hormone (GnRH) synthesis [8]. GnRH deficiency result in delayed puberty and pronounced hypogonadal features [5]. There is associated anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia. Usual presentation is due to abnormal phenotype including micropenis, loss of voice change, absence of pubic and axillary hair distribution and infertility.

Our patient presented with delayed puberty, characterized by absence of facial and axillary hair and sparse pubic hair, micropenis and bilateral small testes. Our patient did not give any history of cryptorchidism.

In a study done by Abujbara et al [9] in 2004, cryptorchidism or a history of cryptorchidism was present in 73% of patients. In KS with cryptorchidism, chorionic gonadotropin therapy improved the cryptorchid state without the need of surgery [10].

Magnetic resonance imaging is the main radiological investigation performed to assess the olfactory bulb and helps to diagnose Kallmann syndrome earlier. Olfactory bulbs are normally seen as well-defined structures situated either side of the lower end of olfactory sulcus and the olfactory sulci are seen between the gyrus rectus and medial orbital gyrus which is best visualized in thin section coronal T2WI (figure 1). The main finding in KS is the absence of olfactory bulb [11]. Other MRI findings are bulb hypoplasia, hypoplastic olfactory grooves and absence/hypoplasia of olfactory girdle, hypoplasia of the rectus gyrus and flattening of the fovea [12]. MRI examination in our patient revealed absence of bilateral olfactory bulbs and grooves, absence of the olfactory sulcus resulting in fused gyrus rectus and medial orbital gyrus (figure 2) and associated partial empty sella (figure 3).

In KS hormonal evaluation shows low serum testosterone and low levels of the gonadotropins LH and FSH. When the human chorionic gonadotropin (HCG) challenge tests are performed there is an increase in serum FSH, LH values and testosterone values which gives the biochemical diagnosis of KS [12]. In our patient we found low level of testosterone, LH & FSH and normal levels of TSH, PRL and cortisol.

There are several anomalies associated with KS such as craniofacial asymmetry, cleft palate, harelip, color blindness, congenital deafness, empty sella, aplasia/hypoplasia of the adenohypophysis and unilateral renal anomalies [5]. In our patient we only found partial empty

sella. Differential diagnosis may include functional and structural causes of hypogonadotropic hypogonadism.

Treatment of the hypogonadism due to androgen deficiency is treated with testosterone. Hormone replacement therapy given to restore virilization and secondary sex characters .To restore fertility, treatment with pulsatile GnRH can be used [5]. Other treatment modalities are used according to associated clinical problems. There is presently no treatment for hyposmia as it is due to the pathology in the olfactory bulbs.

CONCLUSION

We presented a rare case of KS, presenting with poor development of secondary sexual characteristics and decrease smelling capacity. Hormonal evaluation revealed low levels of testosterone, LH & FSH and normal levels of TSH, PRL and cortisol which was consistent with hypogonadotropic hypogonadism. MRI revealed absence of bilateral olfactory bulbs and grooves, absence of the olfactory sulcus which are always absent among patients suffering from kallmann syndrome. We planned to manage further this case with Hormonal replacement therapy to induce puberty and later on when fertility will be desired, pulsatile GnRH will be administered.

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