Kallman Syndrome

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Abstract
Kallman syndrome (KS) is a rare genetic disorder characterized clinically by failure to attain puberty or failure to fully complete it along with an absent or impaired sense of smell with absence of bilateral olfactory bulb and sulci along with absent olfactory tracts. Only very few cases of Kallman syndrome have been reported in females in Indian population.

Introduction
Kallman syndrome was first recognized in the nineteenth century by a Spanish pathologist Maestre de San Juan and later redefined by Kallman and Schoenfeld in 1944, who showed the co-segregation of anosmia and hypogonadism in affected individuals from three families and therefore established the hereditary nature of this syndrome. Clinically, it is characterized by delay or absence of signs of puberty along with an absent or impaired sense of smell. Radiologically, it is characterized by absence of bilateral olfactory bulb and sulci along with absent olfactory tracts. It is usually diagnosed in adolescence due to delay in the onset of physical changes associated with puberty. Here we describe a 19 year old female with characteristic clinical and radiological findings suggestive of Kallman syndrome.

Case Report
A 19 year female presented with chief complaints of non-initiation of menstruation along with incomplete development of breast, axillary and pubic hair. Patient also had lack of sensation of smell. Birth history of the patient revealed that she was born of a non-consanguineous marriage, as a full-term normal delivery with normal perinatal course. She had normal growth (height) but had developmental milestones, attained normal growth (height) but had incomplete breast development along with scanty axillary and pubic hair. Patient also had lack of menstruation along with incomplete breast development along with scanty axillary and pubic hair. Both parents of patient are alive with no comorbidity. So are patient’s elder sister aged 21 and younger brother aged 17. On examination, patient had a pulse rate of 92 /min, and blood pressure of 130/80 mm Hg in right arm in supine position. Pallor, icterus, cyanosis, clubbing, lymphadenopathy were absent. Patient had a height of 167 cm and weight of 45 kg and BMI of 16.13. Her breasts, axillary and pubic hair were at stage 3 Tanner. On olfactory examination, sense of smell was found to be absent in bilateral nostrils. Rest of the neurological examination was normal. Systemic examination of respiratory, cardiovascular and abdominal system was normal. On laboratory investigations, complete haemogram, liver and renal function tests were normal. Patient’s serum estradiol was 13.20 (40 - 410) pg/ml, FSH < 0.50 (1.5-33.40) mIU/ml and LH 0.35 (1.90-76.30) mIU/ml i.e. levels were below normal while prolactin 7.28 (1.8-20.30), thyroid [T3 - 1.10 (0.8-2.10), T4 - 8.50 (5.01-12.45), TSH - 1.19 (0.7-6.4) ng/ml], cortisol 9.13 (4.46-22.7) mcg/dl and ACTH 29.8 (0-40) mcg/dl levels were within normal range. Echocardiography, audiometry and test for color vision revealed no abnormality. Patient was found to be having osteoporosis on bone densitometry test. Magnetic resonance imaging of brain (Figure 1) showed absence of bilateral olfactory bulb and sulci. Based on the characteristic clinical and radiological findings, patient was diagnosed as a case of Kallman syndrome and she was treated with combination oral contraceptives. Patient had initiation of menstrual cycles following this therapy. Patient is presently doing well and is on regular follow up.

Discussion
Kallmann syndrome is a rare genetic disorder characterized by the association of hypogonadotropic hypogonadism and anosmia. Anosmia is associated with underdevelopment or absence of the olfactory bulbs and tracts, and hypogonadism results from impaired secretion of GnRH. It affects 1 in 10000 males and is five times less commoner in females. The genetics of KS remains poorly understood. Three different inheritance patterns have been reported in familial cases, namely X chromosome-linked (KAL-1), autosomal dominant (KAL-2), and autosomal recessive (KAL-3).\textsuperscript{1} However, most cases are sporadic. In this case, no relative was found to be associated with this condition.

During the fetal period, Gonadotropin releasing hormone (GnRH) neurons originate in the olfactory placode (i.e. the early developing nose), then migrate along the fetal olfactory (smell-related) neurons that also originate in the nose and eventually enter the brain ultimately reaching their way to the

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hypothalamus, their ultimate residence during early gestation. In both sexes, these GnRH neurons are fully active and functional, secreting GnRH soon after birth (neonatal period) and begin to secrete GnRH in a characteristic pulse pattern. Kallmann syndrome occurs when the hypothalamic neurons that are responsible for releasing gonadotropin-releasing hormone fail to migrate into the hypothalamus during embryonic development resulting in this unique combination of GnRH deficiency and anosmia (due to loss of olfactory neurons), that define this clinical syndrome. Other associated anomalies including various cardiovascular abnormalities, renal agenesis, synkinesis, hearing loss, color blindness, short fourth metacarpal and facial anomalies had been reported in patients with KS. In this case, no anomalies were noted.

Treatment of patients with Kallman syndrome who do not desire fertility is gonadal steroidal replacement therapy viz, estrogen and progesterone in females and testosterone in males. Estrogen replacement therapy in females with Kallmann syndrome promotes the development of secondary sexual characteristics, including breast development and menstrual function, and it may prevent osteoporosis. Oral contraceptives may be used as replacement therapy in young women.

Patients who desire fertility may be administered gonadotrophins by using a portable infusion pump to deliver subcutaneous pulsatile GnRH. Assisted reproductive technologies, including IVF, ZIFT, GIFT, and intracytoplasmic sperm injection (ICSI), have been used successfully.

Conclusion

Physician should be aware of this disease which has a rare occurrence in females, especially in scenarios where fertility is an issue.

References