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Olfactory Agenesis in Kallmann Syndrome (KS)

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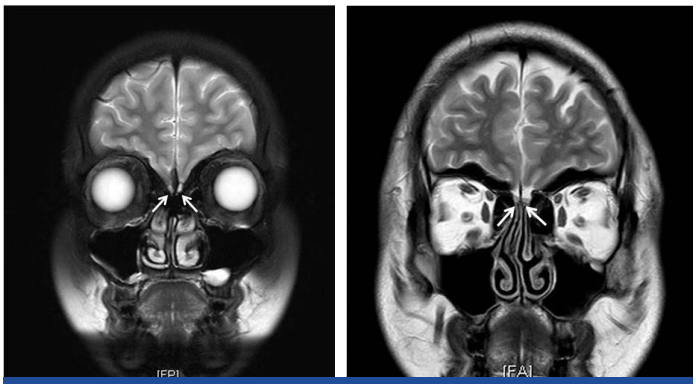
Kallmann syndrome (KS) is a heterogeneous genetic disorder characterised by isolated gonadotrophic deficiency and anosmia. Defective migration of GnRH neurons along with olfactory neurons results in hypoplasia or agenesis of olfactory bulb and or sulci and gonadotrophin deficiency. We hereby report a young female who presented with features of hypogonadism and anosmia.

A 17-year-old female presented to our endocrine clinic with primary amenorrhea. She was born of non-consanguineous marriage and her birth history was unremarkable and developmental mile stones were normal. On questioning, she admitted to the fact that she was not very appreciative of smell from the childhood when compared to other family members. Her stature was at par with her peers and there was neither a history of any chronic illness nor any medication. She had one male elder sibling whose growth and pubertal development were normal according to age. On examination, her height was 162 cm with a mid-parental height of 159 cm. There was no pallor or oedema or thyromegaly. There were no dysmorphic features. Her Tanner staging for breasts was prepubertal (Tanner 1) and pubic hair was also Tanner stage 1. Cardiovascular, respiratory and neurological examinations were within normal limits. Her blood investigations were as follows: TSH – 2 uIU/ml (Normal: 0.8-4), FT4-1.1 ng/dl (Normal: 0.8-1.8), FSH-0.2mIU/ml, LH-0.2mIU/ml, Prolactin-12 ng/ml (Normal<20), morning cortisol -16 µg/dl (Normal: 12-15), Hemoglobin- 13.2 gm/dl, Creatinine- 1.1 mg/dl (Normal: 0.8-1.3).



[Table/Fig-1]: MRI brain of the patient showing absence of olfactory sulci and bulb
[Table/Fig-2]: MRI brain of a normal subject displaying olfactory sulci and bulb

She underwent MRI scanning of the brain [Table/Fig-1] which revealed the absence of olfactory bulb and olfactory sulci [Table/Fig-1]. The MRI brain of a normal subject is shown in [Table/Fig-2] for comparison. Her low gonadotropin levels in the absence of normal pubertal development and imaging features were suggestive of KS, a form of hypogonadotropic hypogonadism. There were no skeletal or renal abnormalities. She was initiated on cyclical oestrogen – progesterone pills with which she developed secondary sexual characters along with menstrual bleeding at one year follow up.

KS is a heterogeneous genetic disorder which include hypogonadism and anosmia due to hypoplasia or agenesis of olfactory bulb and sulci along with GnRH deficiency [1]. It is a genetically heterogenous condition, with X-linked, autosomal dominant and recessive modes of inheritance due to mutataions in KAL 1, FGF 8/ FGFR1 and PROK2/ PROK2R respectively [2]. The X linked forms may be associated with other phenotypic features. The autosomal forms of KS (A-KS) exhibit no consistent phenotype apart from gonadotropin deficiency and anosmia, although a heterogeneous collection of defects are seen in a minority of cases. The associated defects include cleft palate or other craniofacial and dental defects, unilateral renal agenesis or aplasia; cryptorchidism, micropenis, neural hearing defects and synkinesis or mirror movements of hand [3]. Since GnrH pulsation studies may not be possible at all centres, MRI with 1 mm cut is an important diagnostic tool for diagnosis of KS. Management of these subjects include screening for associated anomalies and monitoring for progressive worsening secondary to organ defects. The goal of the treatment is two folds. First, hormone replacement therapy is needed to induce puberty and to maintain gonadal hormones at near normal physiological levels till fifth decade of life. Secondly, fertility treatment involves administering gonadotrophins to induce ovulation.

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