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CASE REPORT

# An adolescent with Kallmann syndrome: A case report

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Kallmann syndrome, hypogonadism, adolescent, olfaction disorders.

## Abstract

**Introduction:** Kallmann syndrome (KS) is characterized by the combination between hypogonadism and anosmia. Hypogonadism can be diagnosed during childhood by identifying cryptorchidism and/or micro penis or during adolescence due to pubertal delay considering the absence of secondary sexual characteristics. **Case Report:** To describe the clinical findings regarding teenagers diagnosed with KS, monitored since childhood, emphasizing the prevalent aspects as well as the clinical consequences associated to it. **Conclusion:** Clinical abnormalities during childhood such as cryptorchidism and anosmia or puberal delay should be considered warning signs to start examining and diagnosing hypogonadism and SK, which should lead to clinical practices of Pediatrics and adolescent medicine.

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## INTRODUCTION

Kallmann syndrome (KS) was first described by Maestre de San Juan in 1856 and characterized as a genetic disorder by Franz Josef Kallmann in 1944. In 1969, Bardin et al. found that individuals with KS had low gonadotropin levels. In the last decade, findings from research on the embryogenesis of olfactory sensory neurons and genetic mutations were incorporated to the description and diagnostic criteria assigned to KS, while X-linked, autosomal dominant, and autosomal recessive inheritance patterns were recognized[1-3].

KS is characterized by isolated hypogonadotropic hypogonadism (IHH) associated with olfactory disorders such as hyposmia or anosmia. IHH has been linked to partial or complete lack of puberal development secondary to a defect in the production or secretion of the gonadotropin-releasing hormone (GnRH) in the hypothalamus or to pituitary-induced GnRH resistance[4]. The prevalence of KS varies between 1:10,000 and 1:80.000 in males and was reported as 1:50,000 in females, with males being more affected than females by ratios of up to 5:1[1,5].

Anosmia has been correlated with GnRH deficiency, since the migration and differentiation of GnRH neurons rely on the formation of the olfactory bulb. Olfactory bulb neurons and GnRH neurons stem from the embryonic nasal epithelium, migrate toward the meninges, and cross the cribriform plate. GnRH neurons subsequently move to the preoptic area of the hypothalamus guided by olfactory bulb neuron projections. Therefore, defects in the formation of the olfactory bulb and tract may disturb the migration and differentiation of GnRH neurons[1].

Olfactory bulb aplasia or hypoplasia can be confirmed through magnetic resonance imaging (MRI) of the skull, although this finding has not been correlated with olfactory function. Alterations of inner ear structures, tumors and lesions of the hypothalamus and pituitary can also be picked up with the help of MRI[6].

The following signs of delayed puberty must be considered in individuals suspected of IHH: lack of thelarche by age 13; primary amenorrhea at the age of 15 for girls or a testicular volume smaller than 4 ml for boys aged 14. However, differences pertaining to ethnicity and race may change the parameters and age ranges used in IHH protocols[2,7,8]. In rare occasions, children with cryptorchidism and/or micropenis may also be suspected of IHH.

Individuals with KS may present with other malformations including cleft palate, high-arched palate, renal agenesis, sensorineural hearing loss, color blindness, learning disability[1], and impaired spermatogenesis and fertility[9,10].

About 30% of the patients with Kallmann syndrome have known genetic mutations involving approximately 20 genes. In patients with unidentified mutations, the cause of the condition remains unknown. Research has been conducted to find other genetic alterations that may cause the syndrome[11].

Mutations in the following genes have been reported more frequently: KAL-1 (also known as ANOS1), CHD7, FGF8, FGFR1, PROK2 or PROKR2. KAL-1 mutations have been associated with X-linked KS. Most of the individuals carrying KAL-1 mutations present severe gonadotropin secretion impairment and clinical signs identifiable at birth. FGFR1 mutation has been associated with autosomal dominant KS. As in KAL-1 mutations, FGFR1 mutations present a wide variety of genotypes, variable phenotype expressions within families, and more severe reproductive phenotypes than patients with KS without these mutations. A high prevalence of cryptorchidism and micropenis has been described in males with FGFR1 mutations. Additionally, patients with FGFR1 mutations are more often affected by palate defects and dental agenesis - findings not described in patients with KAL-1 mutation[1,11].

In addition to the classic phenotype associated with KS (hypogonadism combined with anosmia), some carriers of mutations on genes PROKR2 and PROK2 develop isolated hypogonadism or isolated anosmia and may not present other manifestations commonly seen in KS such as bimanual synkinesis, renal disorders, dental agenesis, and face or palate defects[1].

Some patients develop a reversible phenotypic variant and may be treated for hypogonadism with androgen replacement therapy. Results include increased testicular volume, normalization of testosterone levels, and fertility after the discontinuation of therapy.

The establishment of associations between phenotypes and genotypes improves screening, reporting of cases, patient follow-up, and family/patient advice[11].

Lab tests show low levels of sex steroids and normal or decreased gonadotropin levels. Lack of or decreased gonadotropin response to GnRH confirms the diagnosis[1,6].

Treatment is based on sex steroid replacement aimed at resuming normal pubertal development and includes attempts to restore fertility by administering gonadotropin-releasing hormone[12]. Timely treatment is relevant not only to restore metabolic, bone, and sexual balance, but also to mitigate the psychosocial effects connected with KS[11,13].

## CASE REPORT

A full-term male patient weighing 3900 g and measuring 51 cm at birth from vaginal delivery was diagnosed with polycystic kidney disease at the age of two months by the pediatrics and pediatric nephrology teams.

The patient was diagnosed with a left retractile testicle by a pediatric surgeon and was followed until a left orchidopexy was performed when he was seven. He underwent a right orchidopexy when he was nine years old.

In a visit with the pediatrician at the age of nine, the patient complained of diminished sense of smell. He was referred to an otolaryngologist who diagnosed him with anosmia. Skull magnetic resonance imaging (MRI) revealed the patient had hypoplastic olfactory bulbs and shallow olfactory

grooves, along with a normal pituitary gland and a normal pituitary stalk.

He was staged as a Tanner G1P1 upon physical examination at the age of 11, with a testicular volume of 1 ml on both sides and a penis measuring 3-5 cm. His workup did not evince alterations in gonadotropin, testosterone, or estradiol levels: LH < 0.1 mIU/ml (1.7-8.6 mIU/ml); FSH = 0.24 mIU (1.5-12.4 mIU/ml); Estradiol = 7.6 pg/ml (7.63-42.6 pg/ml); HCG < 2 mIU/ml (<10 ml/ml). Bone age assessment by x-ray showed a chronological age of (CI) 10 years and 6 months and a bone age (BO) of 11 years (SD 10 months). His height and weight were 146.5 cm and 37 Kg, respectively. The patient was suspected of Kallmann syndrome and was referred to an endocrinologist. He was tested with testosterone cypionate 50 mg/month for three months.

When assessed at the age of 11 years and 8 months after the end of the test protocol with testosterone, the patient was staged as a Tanner P2, with a testicular volume of 2 ml bilaterally and a penis measuring 5-7 cm. Testosterone was discontinued.

At the age of 13 years and 6 months, the patient was staged as a Tanner G3P2, with right and left testicular volumes of 2 ml and 3 ml, respectively, a penis measuring 5-7 cm, no sign of voice change, and a gain of 6.5 cm in height in one year. His testicular ultrasound was unaltered. X-ray examination indicated the patient had a chronological age of 13 years and a bone age of 12 years and 6 months, with a standard deviation of 10.72 months.

The patient was staged as a Tanner G3P2 at the age of 14, with left and right testicular volumes of 3 ml and 4 ml, respectively, after examination by an endocrinologist. He was started on testosterone cypionate 50 mg/month for three months, and the dose was then increased to 100 mg/month.

The patient was recently staged as a Tanner P4, with left and right testicular volumes of 5 ml and 6 ml, respectively, and a penis measuring 9 cm. His height and weight were 164.5 cm and 54.4 Kg. The patient and his family were advised of the possible effects in spermatogenesis and infertility derived from having Kallmann syndrome. The patient is currently being followed at the Adolescent Health Unit and the Endocrinology Service of our institution.

## DISCUSSION

Although rare, Kallmann syndrome introduces significant repercussions to child and adolescent care, since early diagnosis may trigger the initiation of multidisciplinary clinical care and hormone replacement therapy to treat hypogonadism and/or help the patient cope with persisting alterations such as anosmia and the risk of infertility.

This paper described the case of an adolescent diagnosed with KS who responded adequately to clinical management. Although he was below the age range at which delayed puberty is usually diagnosed, the patient was offered test hormone replacement therapy at the age of 11 on account of clinical manifestations connected with cryptorchidism, renal disorder, and anosmia identified during childhood. While this condition is diagnosed based on clinical parameters, physicians involved in the care of children and adolescents must consider palate, renal, and auditory malformations in their assessment, and the possibility of finding cases of described genetic mutations.

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