CASE REPORT

Kallmann Syndrome with Syndactyly

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Abstract

Kallmann syndrome is a rare genetic disorder marked by hypogonadotropic hypogonadism (HH) and anosmia, affecting 1 in 50,000 females. It is due to a defect of gonadotropin-releasing hormone (GnRH)-secreting neurons migration from the nasal olfactory epithelium to the basal hypothalamus. Non-reproductive, non-olfactory symptoms can also be present, depending on the genetic form of disease. The management includes hormone replacement therapy and fertility treatment. We report a case of Kallmann syndrome in an 18-year girl who presented with primary amenorrhea with poor, secondary sexual characteristics' development, poor sense of smell and syndactyly. The plasma levels of luteinising hormone, follicle stimulating hormone, and estradiol were very low, while chromosome analysis showed 46, XX karyotype. Pelvic MRI confirmed the presence of uterus and ovaries. MRI of brain was normal. Treatment was started with cyclic conjugated estrogen and progestin with good response. She is now on regular follow-up to monitor treatment.

Key Words: *Kallmann syndrome, Hypogonadotropic hypogonadism, Syndactyly.*

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INTRODUCTION

Kallmann syndrome (KS) is a rare genetic disorder marked by hypogonadotropic hypogonadism and anosmia. It occurs at a rate of 1 in 10,000 males and 1 in 50,000 females, but its prevalence might be underestimated, particularly in females.[1] It was characterised as a hereditary condition by Franz Josef Kallmann in 1944. Its neuropathological description was provided by Georges de Morsier, especially defect of gonadotropin-releasing hormone (GnRH)-secreting neurons' migration from the nasal olfactory epithelium to the basal hypothalamus.[1,2] We, herein present a case of an 18-year female who was diagnosed with this condition and has shown improvement on therapy.

CASE REPORT

An 18-year female was referred to our department with the complaint of primary amenorrhea. She was born of a non-consanguineous marriage and her birth history was unremarkable. She had undergone surgery for syndactyly in her childhood, and presented hyposmia without any history of chronic illness or any medication. She did not report any alimentary disorder or high physical activity. Her spontaneous partial pubarche and thelarche occurred at 13 and 15 years, respectively. On examination, she was 50.4 kgs, 1.57 m tall and had 20.4 kg/m2 body mass index (BMI), with no galactorrhoea or thyromegaly and no evidence of dysmorphism except syndactyly between the first and second toes treated in childhood and between the third and fourth toes (Figure 1). Pubic hair and breast developments were Tanner stage II and III, respectively (Figure 2). Cardio-vascular, respiratory, neurological and ophthalmic examinations were all normal. Basal hormonal evaluation revealed low serum estradiol (5.6 pg/ml), luteinising hormone (LH) (0.2 IU/L) and follicle-stimulating hormone (FSH) (0.4 IU/L) levels. While serum testosterone, prolactin level, and thyroid profile were within normal limits as well as anterior pituitary function. Her bone age was 12-13 years. No abnormalities were noticed on abdominal ultrasound examination. Pelvic magnetic resonance imaging (MRI) revealed infantile uterus and small ovaries. Her bone mineral density showed osteopenia. MRI of the hypothalamic-pituitary region showed olfactory bulbs to be present and there was no pituitary or hypothalamic lesion. There were no other skeletal or renal abnormalities. Karyotype revealed normal female pattern (46, XX). The olfactometry was not done because it is not available in our country. The low gonadotropin levels, the absence of normal pubertal development, imaging features and history of syndactyly were suggestive of KS. She was initiated on cyclical oestrogen-progesterone pills with 0.02 mg ethinylestradiol and 0.15 mg desogestrel for 21 days each 28 days. Evolution under treatment was marked by the appearance of menstruation, pubic hair, and breast development evaluated as Tanner stage IV and III, respectively. Her weight was 54.4 kgs with a BMI of 21.95 kg/m^2 in 5 months of treatment. The patient also reported improved self-esteem.

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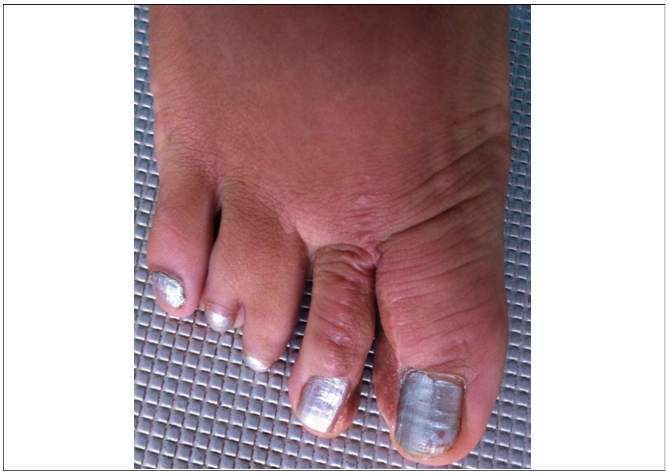

Figure 1: Syndactyly between the first and second toes and between the third and fourth toes.

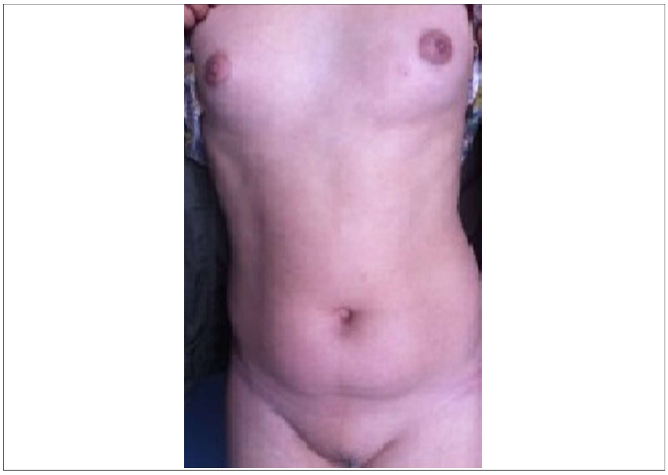

Figure 2: Pubic hair and breast developments were Tanner stage II and III, respectively.

DISCUSSION

KS is a genetically heterogeneous disorder. One-third cases are inherited as autosomal dominant, autosomal recessive, or X-linked mode; while remaining two-thirds are sporadic and may represent new mutations.[3] In fact, more than 15 genes have been linked to the disease.[4] Most individuals with KS are identified at puberty, usually due to incomplete development of secondary sexual characteristics. However, the degree of affected sexual maturation can vary.[4] On the other hand, non-reproductive, non-olfactory symptoms can also be present, depending on the genetic form of disease, such as midline cranial anomalies (cleft lip, cleft palate and imperfect fusion), dental agenesis, skeletal anomalies of the hands or feet (syndactyly or polydactyly), mirror movements of the upper limbs (imitation synkinesis for contralateral limbs), optic problems (colour blindness or optic atrophy), and deafness.[1,5] Our patient presented at 18 years of age with primary amenorrhea with breast development and pubic hair both at Tanner stage II and III, respectively, hyposmia and syndactyly. Clinical diagnosis is important, but may be difficult in patients of prepubertal age and may require MRI and genetic testing.[1,3] In fact, MRI of brain may reveal complete agenesis of olfactory bulbs and sulci or shallow olfactory sulci in about 75% patients.[1,3] Our patient had intact olfactory bulbs on MRI. Management of these subjects includes screening for associated anomalies and monitoring for progressive worsening secondary to organ defects.[3] Certain digital bony abnormalities (*e.g.* of syndactyly) were unique to the FGF8/FGFR1 mutations, presumably reflecting the critical role of FGF signalling in limb formation.[5] The treatment depends on the goal of therapy. First, hormone replacement therapy (estrogen-progestin therapy) is needed to induce puberty and maintain secondary sex characteristics.[1,3] Secondly, fertility treatment involves inducing ovulation with combined gonadotropin therapy or pulsatile GnRH therapy. If conception fails, *in vitro* fertilisation may be an option.[1,3]

PATIENT'S CONSENT:
Informed consent was obtained from the patient to publish the data concerning this case.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
FK: In charge of the patient and authored the manuscript.
MB, MMH: Supported in writting the manuscript.

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