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Case Report

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A rare case of Kallmann syndrome with bimanual synkinesis

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Abstract

Kallmann syndrome is a rare inherited disorder characterized by hypogonadotropic hypogonadism and anosmia or hyposmia. Such cases are mostly diagnosed in adolescent period with complaints of failure to achieve puberty. Early diagnosis and treatment can restore secondary sexual characteristics in such patients. We report a case of a 17-year-old male with Kallmann syndrome who came with hypogonadism and bimanual synkinesis.

Keywords: Hypogonadism, Anosmia, Hyposmia, Bimanual synkinesis

INTRODUCTION

Kallmann syndrome is a rare genetic disorder characterized by failure of an individual to enter puberty. This condition can be associated with a number of phenotypical abnormalities. Precise epidemiological data is lacking due to difficulty in the diagnosis of the condition and gross variation in the phenotypic presentation of the syndrome. There are very few case reports describing adolescents with Kallmann syndrome with delayed puberty and bimanual synkinesis.

CASE REPORT

A 17-year-old boy presented with short stature, absence of secondary sexual characters and inadequate weight gain. Birth history was normal and there was no developmental delay in milestones. Both parents and one brother achieved puberty at normal ages and have normal height. On examination, patient was thin built with normal vitals. No pallor, icterus, clubbing, cyanosis and lymphadenopathy were noted. He had a nasal voice, lipomastia and did not have axillary and pubic hair. Testicular volume was 1ml in both testes. Stretched penile length was 4.3cm. He also had bimanual synkinesis. He had a weight of 42 kg (Z score -1.35), height of 156 cm (Z score -0.16), MPH of 162.5 cm (within target range), arm span/height ratio - 1.01 (No eunachoid habitus), BMI of 16.4kg/m ^{2} (Z score -1.42) and bone age of 13 years 6 months (Greulich and pyle's atlas method). Systemic examination was normal. He also had hyposmia, which the parents and the boy were unaware of and which was verified by testing for different types of smells in each nostrils with

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eyes closed. He could identify odors from lemon, perfume and scented soap but couldnt identify odors from coffee, turmeric and alcohol sanitizer. On laboratory investigations, complete haemogram, serum electrolytes, liver and renal function tests were normal. Serum Testosterone (14.48 ng/dL), FSH (0.87 μIU/dL) and LH (0.14 μIU/dL) were prepubertal level. Cortisol (14.12 μg/dL), Prolactin (16 ng/mL), DHEAS (342.3 μg/dL) and Thyroid function test were normal. Vitamin D level (10.3ng/mL) was low. Echocardiography, ultrasonography abdomen, audiometry, ophthalmological examination was normal. Patient was found to have inappropriately low BMD for age on bone densitometry scan (L1 to L4 spine and total body Z score of-4 and -2.9 respectively). MRI brain with pituitary cuts revealed absent olfactory bulbs and hypoplastic olfactory sulci (Figure 1). Pituitary gland was normal.

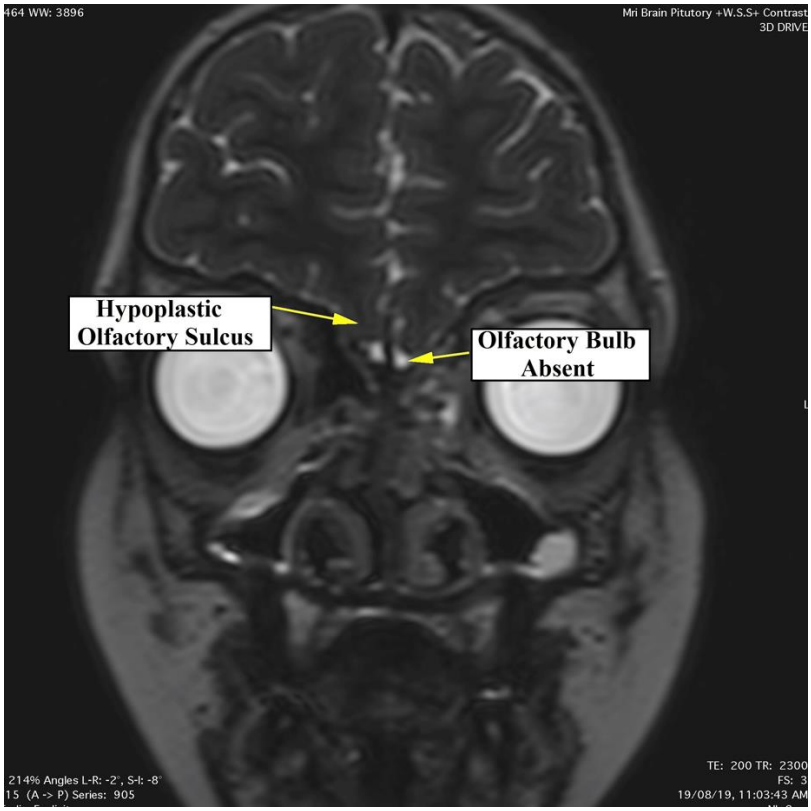

Figure 1: Magnetic resonance imaging of brain (T2) showing absence of bilateral olfactory bulb and hypoplastic olfactory sulcus on coronal section

Based on the characteristic clinical and radiological findings, patient was suspected to have Kallmann syndrome and genetic test was done which revealed pathogenic variant, hemizygous, X linked recessive with microdeletions in the Xp22.31 region (KAL1 gene). He was started on Testosterone depot injection initially with a dose of 50mg/month intramuscular for 3 months, slowly increased and later to 250mg/month and Vitamin D supplementation. He has been counselled that he will develop secondary sexual characters after testosterone treatment but fertility won't be restored. He will require further LH and FSH based therapy to restore his fertility. On regular follow up, the patient was found to have developed pubic hair after 1 year of testosterone injections.

DISCUSSION

Kallmann syndrome is a rare genetic disorder characterized by Hypogonadotropic

Hypogonadism with anosmia or hyposmia resulting from agenesis or hypoplasia of the olfactory lobes or sulci, or both. It is associated with Gonadotropin releasing hormone (GnRH) deficiency, characterized by complete or partial absence of any endogenous GnRH-induced LH pulsations [1]. GnRH neurons usually migrate along olfactory axons. In the absence of olfactory bulbs, this migration is disrupted leading to hypogonadotropic hypogonadism. This clinical condition was first reported by Maestre de San Jaun, a Spanish anatomist in 1856 [2]. Later, in 1944, an American geneticist, Kallmann reported a study of hypogonadism and anosmia occuring in three families. It affects 1 in 30000 males and is five times less common in females [3]. Modes of inheritance reported are autosomal dominant, autosomal recessive and X linked recessive. Five genes have been identified namely KAL1, FGFR 1, PROKR2, PROK2 and FGF8 [4]. Signs and symptoms can be split into two different clinical categories - Reproductive features involve failure to achieve puberty, small penis, small testes, primary amenorrhoea, poorly defined sexual characters and infertility. Non reproductive features involve anosmia, hyposmia, cleft palate, cleft lip, choanal atresia, icthyosis, seizure disorder and neurosensory hearing loss. Unilateral or rarely bilateral renal agenesis or aplasia, horseshoe kidneys and mirror movements of the hands (synkinesia) are limited to X-linked form [1][5]. According to the presence of certain accompanying clinical features, genetic screening for particular genes may be prioritized: Synkinesis (KAL1), dental agenesis (FGF8/FGFR1), bony anomalies(FGF8/FGFR1), and hearing loss(CHD7) [6]. Patients with KAL1 gene have a significantly higher prevalence of Synkinesia (43%) compared with non KAL1 gene patients (12%) [7]. KAL1 is located at Xp22.3 and is the most common mutated gene causing Kallmann syndrome in 10% of patients [8]. This gene encodes for anosmin-1 which is an embryonic component of the extracellular matrix and is involved in GnRH induced olfactory neurons migration from the olfactory placode to the hypothalamus during embryonic life. Mutations in KAL1 usually induce severe reproductive phenotypes including absent puberty and high frequency of cryptorchidism or microphallus [9]. Serum testosterone, Luteinizing hormone and follicle stimulating hormone levels are usually low. MRI scan of brain shows a hypoplastic olfactory sulcus with absence of olfactory bulb in most of the cases.

Testosterone is given in males to restore virilization and secondary sexual characters as part of replacement therapy. In females combined estrogen and progesterone are used. Pulsatile treatment with Gonadotropin Releasing Hormone is usually used to restore fertility. Reversal of symptoms have been reported in between 10% to 22% of cases (Except anosmia) [7] The article highlights how early diagnosis and timely intervention is the key in management of Kallmann syndrome patients and thus can restore secondary sexual characters and fertility and save them from a lot of health problems.

Author declaration

Author Contributions
Rajesh Joshi investigated and diagnosed the case. Aniket Deshmukh collected articles on kallmann and prepared this manuscript. Both authors read and approved the final manuscript.

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Ethics approval and consent to participate
Patient actively have given a written informed consent.

Competing interests
None

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