

Kallmann's Syndrome: A Rare Cause of Primary Amenorrhoea

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Abstract

Kallmann syndrome is a very rare hereditary disease. It is characterized by hypogonadotropic hypogonadism in association with anosmia or hyposmia, both of which occur as a result of impairment of olfactory axon development and failure of migration of gonadotropin-releasing hormone (GnRH) neurons. Mode of inheritance can be autosomal dominant, autosomal recessive, or X-linked. We report a case of Kallmann syndrome in an 18 year old girl who presented with primary amenorrhoea, poor sexual development with poor sense of smell and colour blindness. Plasma levels of LH, FSH and oestradiol were very low. The patient's other pituitary hormone levels were normal. Chromosome analysis showed 46, XX karyotype. USG of lower abdomen confirmed presence of uterus and ovaries. MRI of brain showed olfactory bulbs to be present and there was no pituitary or hypothalamic lesion. We present this case for its very rare occurrence in the eastern part of the world and the typical feature being normal MRI brain with functional defect of the olfactory pathway. Treatment was started with cyclic conjugated oestrogen and progestin. Our patient is now on regular follow-up to monitor response to treatment.

Keywords: Kallmann syndrome; Primary amenorrhoea; Anosmia

Introduction

Kallmann Syndrome (KS) is a form of hypogonadotropic hypogonadism characterized by delayed or absent puberty and an impaired sense of smell [1-5]. It is a rare genetic condition affecting 1 in 10,000 males 1 in 50,000 females [2,4]. Either anosmia or severe hyposmia is present in these patients and this feature distinguishes Kallmann syndrome from most other forms of hypogonadotropic hypogonadism [1,4,6,7]. The condition usually presents around puberty with impaired pubertal changes. Timely diagnosis and management can be highly beneficial for the affected persons. One such case is described hereby.

Case Report

An 18 year old unmarried girl, Honours student, from a middle class family, presented at out patient department of OBGYN unit of BIRDEM hospital, Dhaka, Bangladesh in January 2014, with history of primary amenorrhoea, poor sexual development, poor sense of smell and color blindness. She gave no history of extreme dieting, sudden weight loss or weight gain, bulimia or rigorous exercise. She was not on any medication.

An USG of lower abdomen was done which confirmed presence of uterus and ovaries. She had progesterone challenge test (Tab. Norethisterone acetate 5 mg TDS for 7 days) to bring on menstruation but did not response. She had no history of any major medical or surgical illness in the past. Her paternal aunt had suffered from primary amenorrhoea. USG and IBU showed no abnormalities regarding kidney, renal pelvis and lower urinary tract in both sides.

On general examination her height was 154 cm and all her vital parameters were within normal limit. Her breast development was poor (Tanner stage II) with no evidence of galactorrhoea. On examination of the external genitalia she had underdeveloped vulva, sparse pubic hair (Tanner stage II), prominent labia minora, flat labia majora and intact hymen. Full endocrine evaluation was done which revealed low levels of serum LH, FSH and oestrogen (1.5 IU/L, 3 IU/L and 40 pg/ml respectively). Serum testosterone, prolactin level and thyroid profile were within normal limit. On oral glucose tolerance test she was non diabetic. Karyotype was done to exclude Turner syndrome which revealed normal female pattern (46 XX). MRI of brain showed olfactory bulbs were present and there was no pituitary or hypothalamic

lesion. The olfactory sulci and bulbs were assessed as normal. Olfactory tests were done through the smell test by giving different smells near nostril. (Sulci were assessed as normal in comparison to rest of cerebral sulci). So she was diagnosed as a case of primary amenorrhoea due to Kallmann's Syndrome (KS). We didn't perform any genetic testing, for the genes known to be involved in GnRH migration through the olfactory bulb. Kallmann syndrome was an anomaly of neuronal migration. Cells that differentiate into Gonadotrophin releasing hormone (GnRH) secreting neurons originate from within embryonic olfactory epithelium and migrate along fascicles of vomeronasal and terminalis nerves into forebrain. This migration of GnRH neurons was arrested in KS resulting in GnRH deficiency (<5 ng/mL) followed by different degrees of luteinizing hormone (LH) and follicle stimulating hormone (FSH) deficiencies. Abnormal development of olfactory placode also resulted in improper development of olfactory bulbs and sulci. Other associated anomalies including various cardiovascular abnormalities, renal agenesis, cryptorchidism, short fourth metacarpal and facial anomalies had been reported in-patients with KS. In our patient, no anomalies were noted.

The patient and her parents were duly counseled regarding her diagnosis, treatment and prognosis. Treatment was started with conjugated oestrogen (Tab. Premarin 2.5 mg daily for 28 days) and progestin (Tab. Medroxy progesterone acetate 5 mg for last 12 days of cycle).

Growth hormone was assessed by growth hormone stimulation tests in order to exclude GH deficiency. Also, the ACTH and cortisol of this case was detected as a similar reason.

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She is now under regular follow up with monitoring of hormone levels and sexual development.

She didn't have any family history of her own mother or siblings or maternal and paternal aunt regarding anosmia and hyposmia. The age of mother's menarche was at 10 years of age.

Discussion

The association of hypogonadism and anosmia was first described by Maestre de San Juan, a Spanish anatomist, in 1856. Later in 1944, a German-American geneticist, Franz Joseph Kallmann, recognized the genetic basis of this condition in three families, and thereafter this association has been known as Kallmann syndrome [8]. KS accounts for nearly two thirds of individuals with isolated GnRH deficiency (IGD). Apart from the sense of smell there is no difference in the diagnosis or treatment of a case of IGD or a case of Kallmann syndrome [1,9].

The molecular pathogenesis of KS is complex but mainly referable to the impairment of olfactory axon development and of the migration of gonadotropin-releasing hormone (GnRH) neurons. Mutations in the genes KAL1, FGFR1, PROKR2, PROK2, CHD7, and FGF8 reportedly cause Kallmann syndrome [1,2,4,10-14]. The genetics of Kallmann syndrome and other forms of hypogonadotropic hypogonadism is still far from clear with around 70% of cases having an unknown genetic origin [15].

Kallmann syndrome is a genetically heterogeneous disorder. Approximately one third cases are inherited. The remaining two thirds are sporadic and may represent new mutations. Three different patterns of inheritance have been described-autosomal dominant (64%), autosomal recessive (25%), or X-linked (11%) [1,4,16]. Of 59 Kallmann syndrome patients analyzed by Oliveira et al. [21] were familial and 38 were sporadic cases [17]. Tagatz et al. described 3 unrelated females with hypogonadotropic hypogonadism and anosmia [18]. No relative was affected and the parents in each case were unrelated. Sato et al. studied 3 female Japanese individuals with Kallmann syndrome who were apparently sporadic cases [14]. In this case the patient had a paternal aunt who suffered from hypogonadotropic hypogonadism and anosmia. Gasztonyi et al. reported a case where the maternal aunt of the affected female had anosmia, making autosomal dominant inheritance likely [19]. Levy and Knudtzon also reported a family in which 2 sisters, aged 13 and 19 years, had hypogonadotropic hypogonadism and anosmia [20].

Most individuals with KS are identified at puberty usually due to incomplete development of secondary sexual characteristics. However, the degree to which sexual maturation is affected can vary [1]. Women with KS typically have Tanner stage I breast development and amenorrhea and have Tanner stage II-III pubic hair, but milder presentations with spontaneous menses are recognized [1,21]. Our patient presented at 18 years of age with primary amenorrhoea with breast development and pubic hair both at Tanner stage II. The patient reported by Persson et al. presented at 16 years and 11 months of age, never having menstruated and with no evidence of breast development or any other sign of spontaneous puberty [22].

Because of the failure of growth plates in the bone to fuse in the absence of sex hormones, most individuals with KS have a eunuchoid body habitus (i.e., arm span exceeds height by ≥ 5 cm). Whereas skeletal maturation is delayed, the rate of linear growth is usually normal with absence of a distinct pubertal growth spurt [23].

The impaired olfactory function in Kallmann syndrome can be either hyposmia or complete anosmia [24]. Most individuals with

impaired smell do not have any physical or social impairment and the finding often goes unnoticed until KS is diagnosed [1,4]. Our patient had complete anosmia like that of Persson et al [22]. In a series of 6 patients reported in Jordan 4 had anosmia and 2 had hyposmia [25]. Additional frequently observed features of KS include both neurological (i.e. synkinesia, and hearing loss) and nonneurological (i.e. renal aplasia and midline craniofacial abnormalities) phenotypes [26-30]. Some patients may also present with color blindness, congenital heart disease and later on with osteoporosis [4]. Franz Kallmann himself reported color blindness in these patients in the pioneer series [31].

The diagnosis is often one of exclusion found during the workup of delayed puberty. For both males and females with constitutional delay of puberty, endogenous puberty will eventually commence without treatment. However a delay in treatment in a case of KS/IGD will delay the physical development of the patient and can cause severe psychological damage. The "wait and see" approach of being a "late bloomer" is probably counterproductive to the needs of the patient whereas a step by step approach with hormone replacement therapy can be used as a diagnostic tool. In females diagnosis is sometimes further delayed as other causes of amenorrhoea normally have to be investigated first before a case of KS/IGD is considered [32].

Laboratory studies show inappropriately low or normal serum concentration of LH (luteinizing hormone) and FSH (follicle stimulating hormone) in the presence of low circulating concentrations of oestradiol in females. Levels of other anterior pituitary hormones (i.e. prolactin, TSH) and thyroid hormones are typically normal [1,4]. The LH, FSH and oestrogen levels of this patient were 1.5 IU/L, 3 IU/L and 40 pg/ml respectively. In another case report basal LH concentration was <1 IU/L and basal FSH level was at 0.8 IU/L. The anterior pituitary reserve was otherwise normal on dynamic testing [22]. Hormone levels of the patients reported by Abu Jbara et al. showed basal LH and FSH levels of 0.5-0.8 IU/L and 1.2-2.6 IU/L and oestradiol level was 5-15 pg/ml [25].

Imaging studies MRI of brain may reveal abnormal olfactory systems, including complete agenesis of olfactory bulbs and sulci or shallow olfactory sulci in about 75% patients [1,4]. This patient had intact olfactory bulbs on MRI. Several case reports are available for male patients with Kallmann syndrome with olfactory bulb abnormality as it is five times commoner in male [33-35]. Whereas only one case of a female adolescent with KS presented by Novo et al. was found who had hypoplasia of the nasal sulcus and agenesis of the olfactory bulbs [36]. The case reported by Persson et al. had no abnormality of the pituitary, upper thalamus or olfactory pathway [22].

Assessment for presence of possible non-reproductive features includes renal ultrasound examination (to detect unilateral renal agenesis), hearing tests (to detect sensorineural hearing loss), skeletal survey (to detect limb/spine bony abnormalities), dental exam (to detect dental agenesis), eye exam (to detect iris and/or chorioretinal coloboma), Ishihara chart testing (for colour blindness), echocardiogram (to detect congenital heart disease) and developmental assessment (if there is evidence of developmental delay). In addition potential deterioration in bone health that may have resulted from periods of low-circulating sex hormones needs to be addressed. To assess osteoporosis bone densitometry is done by dual-energy radiographic absorptiometry (DXA) [1,4].

Other tests include progesterone challenge test either with progestin or with combined oestrogen-progestin. Women with a profound lack of oestrogen are unlikely to respond to progestin alone. Lack of withdrawal bleeding even with combined oestrogen-progestin

suggests the presence of abnormal endometrium (including uterine synechiae) or outflow obstruction [4].

Olfactory function is evaluated by history and by formal diagnostic smell tests, such as the University of Pennsylvania Smell Identification Test (UPSIT), that evaluates an individual's ability to identify 40 microencapsulated odorants and can be easily performed in most clinical settings [37-41]. Anosmia, hyposmia, or normosmia is identified using the UPSIT manual normogram, which incorporates an individual's score, age at testing, and gender. Individuals with IGD with either self-reported complete anosmia or a score of hyposmia/anosmia on UPSIT testing are diagnosed with KS, while those with normal olfactory function are diagnosed with normosmic IGD (nIGD) [42].

For treatment behavioral modification and psychological counseling of the patient and her family is of utmost importance [4]. Treatment for KS and other forms of HH can be split into two different categories-hormone replacement therapy and fertility treatments [43,44].

Hormone replacement therapy for females not desiring fertility-although a definitive diagnosis of KS in females is usually made around age 18 years, occasionally, a high clinical suspicion may be present in an adolescent presenting with anosmia and delayed puberty and therapy may need to be initiated earlier (age ~14 years). To allow optimal breast development, initial treatment should consist of unopposed estrogen replacement via oral or topical preparations (Tab. Premarin 0.3 mg daily to be increased gradually to an adult replacement dose of 1-1.25 mg daily). Once breast development is optimal, a progestin should be added for endometrial protection (cyclical progestin daily for 10-12 days) [1].

Hormone replacement therapy for females desiring fertility-to stimulate folliculogenesis, either combined gonadotropin therapy (hCG and human menopausal gonadotropins [hMG] or recombinant FSH [rFSH]) or pulsatile GnRH therapy may be given. If conception fails, in vitro fertilization (IVF) may be an option [1].

Optimal calcium and vitamin D intake should be encouraged and specific treatment for decreased bone mass with bisphosphonates should be considered depending on the degree of bone mineralization for prevention of osteoporosis [1].

Patient education is an integral part of management of KS. These patients can survive for lengthy periods in the absence of associated life-threatening conditions. They must be aware of the risks and benefits of gonadal steroid replacement therapy. They should be informed that current therapies permit fertility in most patients with Kallmann syndrome and although Kallmann's Syndrome is usually life-long condition, spontaneous recovery of gonadal function is possible in some individuals.

From patient's perspective we must realize that having Kallmann syndrome can have a profound effect on a person's life. Not going through puberty at the normal age can produce a huge effect on a person's social development as well as physical development [45].

Age of diagnosis and treatment is a big key to how well an individual patient copes with the condition. The patients that cope better with Kallmann syndrome on the whole are those that are diagnosed before the age of 16 and have prompt treatment. Outwardly there is nothing striking about a person with Kallmann syndrome. They will not look any different from anybody else. Once treatment is started and normal hormone levels are restored there are no side effects or life expectancy

issues associated with having Kallmann syndrome.

Morphological abnormalities of olfactory apparatus in KS are best evaluated with MRI. Suzuki et al was the first to describe the visualization of olfactory bulbs and tracts on MR scans [46]. Olfactory bulbs are optimally visualized in coronal planes. Olfactory bulbs are seen as well-defined structures along cribriform plate. Olfactory sulci are seen between Gyrus rectus and medial orbital gyrus. High resolutions coronal fast spin echo T2W and T1W images are the preferred sequences for morphologic evaluation of the olfactory system [47-49]. Reported abnormalities include hypoplastic/aplastic olfactory sulci and olfactory bulb [50-52]. In our study, all patients had abnormalities involving olfactory sulci and olfactory bulb. In addition, two patients had hypoplastic anterior pituitary gland. Hypoplasia of anterior pituitary may be secondary to limited stimulation due to absence of hypothalamic GnRH neurons. Same findings we found in our patient.

Thus, it is necessary to diagnose Kallmann's syndrome at appropriate time, as timely replacement can restore secondary sex characters and fertility. In this way, patient and his or her family can be saved from a lot of psychosocial problems.

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