

Clinical and Inheritance Profiles of Kallmann Syndrome in Jordan

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ABSTRACT

Background: Proper management of patients with kallmann syndrome allows them to attain a normal reproductive health. The purpose of this study is to demonstrate the presentation modalities, phenotypes and the modes of inheritance among 32 patients with Kallmann syndrome in Jordan, which would facilitate recognition of the syndrome with prompt management and provision of genetic

Subjects: Over a period of five years (1999-2004), the clinical and inheritance profiles of 26 male and 6 female patients with Kallmann syndrome from 12 families were evaluated at the National Center for Diabetes, Endocrinology and Genetics in Jordan.

Results: The patients belonged to twelve Jordanian and Palestinian families and their ages at presentation ranged between 4 – 46 years. Nine boys aged 4-14 years presented with cryptorchidism and microphallus, all other males presented with delayed puberty, hypogonadism and/or infertility. The main presentation among six female patients was primary amenorrhea. Intrafamilial variability in clinical phenotype was specifically evident for renal abnormalities and sensorineural hearing impairment. Familial KS was diagnosed in 27 patients belonging to five families with the X-linked mode of inheritance and two families with the autosomal recessive mode of inheritance.

Conclusions: (1) the majority of cases in this study represented the X-linked form of KS, which might point to a high prevalence of Kal 1 gene in the population. (2) Genetic counseling provided to these families helps them in reaching a decision regarding their reproductive options and facilitates the diagnosis of affecteds at an early age. (3) Any child with cryptorchidism and microphallus in our population should be investigated for the possibility of having KS.

Key Words: Kallmann syndrome, Hypogonadotropic hypogonadism, Microphallus, Jordan

BACKGROUND

One of the most common causes of hypogonadotropic hypogonadism is Kallmann syndrome, which is a genetically heterogeneous condition that generally affects one in 7,500 males and one in 70,000 females [1]. No data on the incidence of this syndrome in Jordan or in the Arab world is available. Proper management of KS usually provides a within normal reproductive health for the affecteds. KS has three modes of inheritance, X-linked, autosomal recessive & autosomal dominant [2], in addition to the sporadic form which is the most common [3]. The gene responsible for the X-linked form of the disease is KAL1 gene [4], and encodes a protein

anosmin that is directly responsible for the migration of GnRH neurons and the olfactory nerves from the olfactory system to the hypothalamus [2,5,6]. Males usually present in the second decade with delayed puberty and females present with primary amenorrhea. Prepubertal boys may present with microphallus and cryptorchidism [7,8].

Proper management of patients with kallmann syndrome allows them to attain a normal reproductive health. The purpose of this study is to demonstrate the presentation modalities, phenotypes and the modes of inheritance among 32 patients with Kallmann syndrome in Jordan, which would facilitate recognition of the syndrome with prompt management and provision of genetic counseling.

SUBJECTS & METHODS

Over a period of five years, thirty-two male and female patients from twelve Jordanian and Palestinian families were referred to the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman for evaluation of hypogonadism among adults, or microphallus among children.

Prospective evaluation was performed including pedigree construction and complete clinical examination with special emphasis on assessment of anosmia, the presence of mirror image movements (synkinesia) and examination of external genitalia. Neurosensory hearing impairment was assessed by audiometry, renal abnormalities by renal ultrasound and congenital heart defects by echocardiography. All patients were tested for color vision and abnormal eye movements. Complete hormonal evaluation including gonadotrophin releasing hormone (GnRH) stimulation test was done for all adult patients. Seminal fluid analysis was done for male patients aged 16 years and above. Radiological studies included brain, pituitary and olfactory tract magnetic resonance imaging (MRI).

The criteria for diagnosis of KS among adults included the presence of anosmia or hyposmia with clinical signs and symptoms of hypogonadism and a testosterone level < 100 ng / dl among males 16 years and older, and estradiol level < 20 pg / dl among adult females, together with low or inappropriately normal gonadotropin level. While among prepubertal males, the criteria included presence of microphallus with anosmia / hyposmia, and / or absent olfactory bulbs on MRI.

Pedigree analysis was used to establish the modes of inheritance of KS in the familial cases. Inheritance in a family was classified as X-linked if only males were affected in more than one sibship connected by females, or if two or more males were affected in the sibship with associated synkinesia. . Inheritance was classified as autosomal recessive if all affected individuals were members of the same generation and included at least one female.

RESULTS

Over a period of five years (1999-2004), thirty-two patients were prospectively diagnosed with Kallmann syndrome in the National Center for

Diabetes, Endocrinology and Genetics (NCDEG) in Amman. The patients belonged to twelve Jordanian and Palestinian families and their ages at presentation ranged between 4 – 46 years. They included 26 males and 6 females with a male/female ratio of 4.34/1. Nine male patients were aged 14 years and younger.

The clinical features among male patients are presented in table (1), and among female patients in table (2).

All adult patients had low serum levels of basal gonadotropins and low testosterone in males or low estradiol in females. They had an inadequate response to LHRH stimulation test before priming, but better response after priming indicating the integrity of the pituitary gonadotrophes. All patients had anosmia / hyposmia

Cryptorchidism was found or previously operated on in 73% and microphallus in 65% of all male patients respectively.

Renal abnormalities including unilateral renal agenesis, malrotated kidney, and horseshoe kidney were detected in 61% of 19 cases with the X-linked form of KS. Two sporadic cases showed renal anomalies. A variable degree of sensorineural hearing impairment was found in 4 of 19 tested patients with X-linked KS, and in none of the other mode of inheritance or the sporadic cases. Olfactory MRI revealed olfactory tract agenesis in 80 % of cases for which the investigation was done in the series (24 out of 32 patients).

Among females diagnosed as KS in this series primary amenorrhea was the main presenting feature.

Pedigrees were constructed for all families. Five cases were sporadic and 27 cases were familial belonging to seven families. Pedigree analysis assigned an X-linked mode of inheritance to 3 families with affected males linked through normal females (families I, II and IV). Family I is the largest family in our series with 11 affected males. Two further families were designated as having the X-linked form of KS because the affected males in one sibship displayed synkinesia (families III and V). Synkinesia has been reported to be associated only with the X-linked form of KS. Two families were designated as having the autosomal recessive mode of inheritance. One family included affected brother and sister with normal consanguineous parents (family IX), while the other family had 3 affected sisters with normal consanguineous parents (family X). Consanguinity rate among parents of all patients was 83 %, with 50 % of all marriages being between first cousins.

DISCUSSION

This study points to the higher proportion of the X-linked form of Kallmann syndrome among all KS cases seen in an endocrine/genetic clinic in Jordan over a period of 5 years. Among 7 families with inherited KS, the X-linked form was the mode of inheritance in 5 families (71% of familial KS). None of the pedigrees was consistent with autosomal dominant inheritance in this series. In the two families with autosomal recessive inheritance, the probability of a non-penetrant autosomal dominant gene in either parent was considered remote because of absence of any relevant family history. The X-linked form of KS has at times been reported to account for only one third of inherited cases [1], and at other times to be the most frequent form [3]. The high proportion of the X-linked form among our cases may represent a high

prevalence of Kal1 gene among Jordanians and Palestinians.

Consanguineous marriages in Jordan are favoured culturally. Among two thousand marriages in the general population, 32% have been reported to be between first cousins [9]. The figure of 50% first cousin marriages among parents of our patients would thus reflect the high consanguinity rate among the population in general.

Among the XR form of KS, 75% of patients were reported to show synkinesia [5]. Synkinesia in X-linked KS has been attributed to an abnormal projection of the corticospinal tract [10]. In our experience, synkinesia was present in 73% of patients with the XR form of KS and was characteristically more pronounced in the younger age group.

Intrafamilial clinical heterogeneity has been reported among family members carrying the same mutation in Kal 1 gene [5]. In this series, intrafamilial variability in renal anomalies was exemplified in family I, the largest family in our series, where eight out of eleven patients had renal abnormalities. Intrafamilial variability was also seen in family III, in which one patient had a malrotated kidney, his brother had a horseshoe kidney while the third brother had no renal anomalies

Sensorineural hearing loss has also been reported to be associated mainly with the X-linked form of KS [11]. The KAL1 gene is expressed in the inner ear from early developmental stages suggesting that the defect underlying the hearing loss in X-linked Kallmann syndrome occurs during the organogenesis period [5]. In our study, sensorineural hearing impairment was only diagnosed among patients with the X linked form of Kallmann syndrome. Four of nineteen tested males (21 %) showed sensorineural hearing impairment with evident intrafamilial variability.

In this series cryptorchidism or a history of cryptorchidism was present in 73% of patients (19/26), and was not related to a specific mode of inheritance or etiology. Microphallus was present among 65% of the patients in this study, with several of other patients reported a history of treatment with testosterone; the exact number of treated patients or the treatment profile could not be precisely determined.

None of the patients with the X-linked form manifested ichthyosis, mental retardation, short stature or ocular albinism, pointing to the underlying aetiology being a mutation in the Kal 1 gene rather than a contiguous-gene deletion syndrome [12].

Kallmann syndrome has a favourable prognosis under proper management. It should thus be considered in any child presenting with cryptorchidism and microphallus. . Since the gonad state is still dormant in childhood, the gonadotropins level is not helpful. Olfactory MRI may be a more useful tool for the diagnosis [13]. Nevertheless, a normal MRI does not rule out Kallmann syndrome as normal olfactory bulbs can be present in up to 25 % of cases [14]. The presence of anosmia/hyposmia and history of delayed puberty or infertility in the family are helpful in establishing the diagnosis. Where diagnosis remains difficult, it is indicated to follow up these children till they reach puberty.

The majority of Kallmann cases in our study satisfied the X-linked mode of inheritance, which might indicate a high prevalence of Kal1 gene in the population. Patients in our series manifested a wide range of phenotypic heterogeneity with intrafamilial variability of clinical manifestations. We

would recommend an evaluation for Kallmann syndrome in any child presenting with microphallus and cryptorchidism in our population. Further studies are needed to establish the prevalence rate of Kallmann syndrome in Jordan and to define the causative mutations.

Competing interests: none declared

Authors' contributions:

All authors were part of the team that evaluated the patients in the study. MAJ and HH drafted the manuscript.

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Table 1: Clinical features of 26 males with kallmann syndrome

| | Age | Eunuchoidal body proportions | High arched palate | Synkinesia | Hearing Impairment | Renal abnormalities | Azoospermia | cryptorchidism | Micropenis |
|--------------------|-----|------------------------------|--------------------|------------|--------------------|---------------------|-------------|----------------|------------|
| Family 1 | | | | | | | | | |
| 1 | 46 | + | + | - | + | - | + | + | - |
| 2 | 14 | + | + | + | + | + | + | + | - |
| 3 | 27 | + | + | + | - | + | + | + | - |
| 4 | 20 | + | + | + | - | + | + | + | - |
| 5 | 20 | + | + | + | - | + | + | + | - |
| 6 | 19 | + | + | + | - | + | + | + | - |
| 7 | 16 | + | + | + | - | + | + | + | - |
| 8 | 14 | NA | + | + | - | + | NA | + | - |
| 9 | 9 | NA | + | + | - | + | NA | + | + |
| 10 | 6 | NA | + | + | - | - | NA | - | + |
| 11 | 4 | NA | + | + | - | - | NA | + | + |
| Family II | | | | | | | | | |
| 1 | 37 | + | + | - | - | - | + | + | + |
| 2 | 24 | + | + | - | ND* | ND* | ND* | + | + |
| 3 | 22 | + | + | - | ND* | ND* | ND* | - | + |
| 4 | 20 | + | + | - | ND* | ND* | ND* | + | + |
| Family III | | | | | | | | | |
| 1 | 14 | NA | + | + | - | - | NA | - | + |
| 2 | 10 | NA | + | + | - | + | NA | - | + |
| 3 | 8 | NA | + | + | - | + | NA | - | + |
| Family IV | | | | | | | | | |
| 1 | 6 | NA | + | + | - | - | NA | + | + |
| 2 | 5 | NA | + | + | - | - | NA | + | + |
| Family V | | | | | | | | | |
| 1 | 20 | + | + | - | + | - | + | - | + |
| 2 | 19 | + | + | + | + | + | + | - | + |
| Family VI | | | | | | | | | |
| 1 | 19 | + | + | - | - | + | ND | + | - |
| Family VII | | | | | | | | | |
| 1 | 37 | + | + | - | - | - | + | + | + |
| Family VIII | | | | | | | | | |
| 1 | 22 | + | + | - | - | + | + | + | + |
| Family IX | | | | | | | | | |
| 1 | 20 | + | + | - | - | - | + | + | + |

NA: not applicable .

ND: not done.

* : lost contact

Table 2: Clinical Features of 6 females with Kallmann syndrome

| | Age | Eunuchoidal body proportions | High arched palate | Synkinesia | Hearing loss | Renal abnormalities | Primary Amenorrhea |
|-------------------|-----|------------------------------|--------------------|------------|--------------|---------------------|--------------------|
| Family X | | | | | | | |
| 1 | 23 | + | + | - | - | - | + |
| 2 | 21 | + | + | - | - | - | + |
| 3 | 18 | + | + | - | - | - | + |
| Family IX | | | | | | | |
| 1 | 18 | + | + | - | - | - | + |
| Family XI | | | | | | | |
| 1 | 30 | + | + | - | - | - | + |
| Family XII | | | | | | | |
| 1 | 18 | + | + | - | - | - | + |

