Clinical case of Kallmann`s syndrome

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Abstract

Kallmann`s syndrome also called idiopathic hypogonadotropic hypogonadism and olfacto-genital dysplasia is genetically heterogeneous and can be transmitted as an X-linked, autosomal dominant or autosomal recessive trait. Its frequency is about 1/ 10,000 in males and 1/50,000 in females.

The syndrome is characterized with combined olfactory deficiency and low gonaditropin-releasing hormone (GnRH) secretion due failure of the fetal GnRH neurosecretory neurons to migrate from the olfactory placode to the medial basal hypothalamus, where they should constitute the GhRH generator. The isolated hypogonadotropic hypogonadism leads to delayed puberty, decreased libido, amenorrhea, erectile disfunction, lack of secondary sex signs.

We represent a 18 years old girl with history of primary amenorrhea and defective olfaction- hyposmy. Physical examination revealed delayed pubertal development. Laboratory findings proved the existing hypogonadotropic hypogonadism, retarded bone age (equivalent to 14 years). There were no other reasons for the above changes. The existing hyposmy combined with the specific biochemical and hormonal changes proved the diagnosis Kallman` syndrome although rare in females.

Introduction. Male hypogonadism with anosmia was first described by Maestre de San Juan in 1856. The designation olfactogenital dysplasia was introduced to emphasize the association between agenesis of the olfactory bulbs and hypogonadism, and the first familial cases were reported by Kallmann and colleagues in 1944 . AAmong affected kindreds, the high male-to-female ratio is consistent with an X-linked trait, although kindreds with apperent autosomal dominant or recessive modes of inheritance with variable penetrance have also been described. Peripheral leukocyte karyotypes are generally normal.

Recognition of the common embryologic origin of GnRH-secreting neurons and the olfactory bulbs led to the identification of a gene KAL, located on the short arm of the X chromosome (Xp22.3), thought to be responsible for Kallmann` syndrome. Subsequent molecular genetic analysis has revealed that this gene codes for a protein with homology to neural cell adhesion molecules, believed to be involved in neuronal migration during embryogenesis .Mutations and deletions of this gene have been shown to be responsible for the X-linked for of Kallman` s syndrome. Till now five genes have been identified to be responsible for the development of the syndrome: FGFR1, FGF8, PROKR2, PROK2, и KAL1.but they can be found only in 20-30% of the patients. Despite the genetic advances much about the Kallmann` s syndrome remains to be elucidated. According to the involved genes the syndrome can be divided to several subtypes:

- **Kallmann syndrome 1** – deletion of ***KAL1*** gene. An X-related trait of inheritance.
- **Kallmann syndrome 2** – mutation of ***FGFR1*** gene.
- **Kallmann syndrome 3 – mutation of *PROKR2gene***.
- **Kallmann syndrome 4 – mutation of *PROK2*** gene.

The leading feature in the clinical picture is the hypogonadotropic hypogonadism leading to delayed puberty, primary amenorrhea and erectile dysfunction combined with anosmy.

Kallmann syndrome occurs at a rate of 1 in 10,000 male births and 1 in 50,000 female births. Even though mutations in the KAL-1 gene on the X chromosome can cause Kallmann syndrome, only 11–14% of patients with Kallmann syndrome have detectable KAL-1 mutations. Autosomal dominant mutations have been described with the FGFR-1 (8p12) gene, sometimes called the KAL-2 gene. This is thought to cause about 10% of cases. However, about 70% of KS cases seem to be the result of autosomal dominant genes, though the identity of those genes is not yet known.Autosomal recessive mutations of the GnRH-receptor gene (4q13.2) have also been reported. This defect appears to produce a wider spectrum of physical symptoms than with the other gene defects, and the defect lies in the ability of the pituitary gland to recognize GnRH, rather than the ability of the hypothalamus to produce GnRH. There is debate about whether this is in fact Kallmann Syndrome, because the GnRH-receptor development is not related to anosmia.There may also be no obvious family history of inheritance (sporadic cases). However, it is possible for Kallmann Syndrome genes to be passed on to children of a sporadic case.

Clinical case. We represent an 18 years old girl with normal weight and size at birth. Normal development in the first year of life , then a retardation of her neurosomatic development was noticed and different examinations were done. A minor deafness was diagnosed. The retardation of her growth continued in comparison with the children of her age. The first pubertal signs were noticed at the age of 14 and presented with sparse pubic hair. Delayed bone age was found. In an effort to differentiate late puberty and some other reasons for low LH and FSH, an LH- RH (100 µgr) was done. It showed normal response of LH and FSH and was interpreted as positive. MRI of the pituitary was done – without any pathologic changes.
Because of the short stature GH was measured and low normal values were found. Then a test with insulin hypoglycemia was done and a normal response of the GH was found, nevertheless a treatment with genothropin was undertaken.
Minor mental retardation was present - IQ 72 by HAWIK – R.
She was admitted in our clinic in other to investigate the reason for the existing hypogonadotropic hypogonadism.
We found an 18 years old girl with BMI- 19.1 kg/m^2 /weight 44 kg; height 155 cm/. Normal proportion lower to upper part of the body . A lot of dispersed nevi on the skin. Her pubertal development was estimated as telarche- 0 and pubarhe-2-3 /by Marshal- Tanner/. Primary amenorrhea. Short VI-th metacarpal bone. Syndactily between the II-III fingers of both legs.
Hormonal results are shown on table 1.
Table 1. Hormonal results of the patient.

Parameter	Units	Values
TSH	pmol/l	1,019
Free T4	pmol/l	17,29

TAT	IU/ml	10
MAT	IU/ml	8,72
Cortisol morning	Nmol/l	349,0
Cortisol afternoon	Nmol/l	168,8
ACTH	Nmol/l	12,74
Prolactine	IU/l	126,30
LH	IU/l	0,0001
FSH	IU/l	0,16
Estradiol	pmol/l	< 5

Very low values of FSH , LH and estradiol were found with normal other hormone values. Except for retarded bone age no other abnormal findings were established /table 2/

Table 2. Image tehniques

X-ray of palms & wrists	05.02.2009	Bone age equivalent to 14 years. Persistent growth plates of the long bones
MRI brain	09.02.2009	Normal
Abdominal sonography	05.02.2009	Normal
Thyroid sonography	09.02.2009	Normal

Conclusion. The primary amenorrhea, hypogonadotropic hypogonadism, delayed pubertal development and bone age, the existing hypoosmy, normal karyotype and no MRI changes led us to the diagnosis Kallmann` s syndrome although much more rare in females. Because no substitution with estrogens was done till now and the achieved height average for her family we introduced a low –dose estrogen replacement therapy to promote pubertal development.