

Kallmann syndrome

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Abstract

Kallmann syndrome combines hypogonadotropic hypogonadism due to GnRH deficiency, with anosmia or hyposmia. Magnetic resonance imaging (MRI) shows hypoplasia or aplasia of the olfactory bulbs. The incidence is estimated at 1 case in 10,000 males and 1 case in 50,000 females. The main clinical features consist of the association of micropenis and cryptorchidism in young boys, the absence of spontaneous puberty, a partial or total loss of the sense of smell (anosmia). Other possible signs include mirror movements of the upper limbs (synkinesis), unilateral or bilateral renal aplasia, cleft lip/palate, dental agenesis, arched feet, deafness. Diagnostic methods consist of hormones evaluation (GnRH stimulation test) as well as qualitative and quantitative olfactometric evaluation. Hormonal replacement is used to induce puberty, and later, fertility. Kallmann syndrome is due to an impaired embryonic development of the olfactory system and the GnRH-synthesizing neurons. Sporadic cases have been predominantly reported. Three modes of inheritance have been described in familial forms: X-linked recessive, autosomal dominant, or more rarely autosomal recessive. To date, only two of the genes responsible for this genetically heterogeneous disease have been identified: KAL-1, responsible for the X-linked form and FGFR1, involved in the autosomal dominant form (KAL-2). Several other genes are to be discovered.

Keywords

Hypogonadotropic hypogonadism, GnRH deficiency, anosmia, KAL-1 gene, FGFR1 gene

Disease name and synonyms

- Kallmann syndrome

- De Morsier syndrome

- Dysplasia olfactogenitalis

- Hypogonadotropic hypogonadism and anosmia

Excluded diseases

Isolated (*i.e.*, without anosmia) gonadotropin-releasing hormone (GnRH) deficiency

Diagnostic criteria / Definition

Kallmann syndrome refers to the association of hypogonadotropic hypogonadism, due to GnRH deficiency, with anosmia or hyposmia. Magnetic resonance imaging (MRI) shows hypoplasia or aplasia of the olfactory bulbs.

Differential diagnosis

There is no convincing evidence that Kallmann syndrome and isolated GnRH deficiency (*i.e.* without a smell disorder) result from similar anomalies of embryonic development.

Incidence

It is estimated at 1 case in 10,000 males and 1 case in 50,000 females.

Clinical description

Kallmann syndrome is characterized by:

- the association of micropenis and cryptorchidism in young boys (inconstant clinical sign);
- the absence of spontaneous puberty (the most frequent clinical indication);
- a partial or total loss of the sense of smell (anosmia).

Other possible signs are:

- mirror movements of the upper limbs (imitation synkinesis for contralateral limbs). This sign is very frequent in the X-linked form of the disease (KAL-1);
- unilateral or bilateral renal aplasia (not viable if bilateral). This anomaly is found in approximately one third of the X-linked cases (KAL-1 form);
- cleft lip/palate (quite frequent in the autosomal dominant form with involvement of the *FGFR-1* gene) or high-arched palate (quite frequent in the KAL-1 form);
- missing teeth (dental agenesis);
- arched feet;
- cerebellar syndrome;
- deafness;
- other more or less well-established associations.

Management including treatment

The treatment consists of hormonal replacement to induce puberty, and later, fertility. Treatment for anosmia is not available.

Etiology

Kallmann syndrome is due to an impaired embryonic development of the olfactory system and the GnRH-synthesizing neurons. Sporadic cases have been predominantly reported compared to familial cases. It is likely due to incomplete penetrance in the dominant forms of the disease, rather than to the high

frequency of *de novo* mutations or to cases with recessive transmission of the disease.

Three modes of inheritance have been described in familial forms:

- X-linked recessive (KAL-1)
- autosomal dominant (KAL-2)
- autosomal recessive (KAL-3)

To date, only two genes responsible for this genetically heterogeneous disease have been identified. The *KAL-1* gene, responsible for the X-linked form, encodes anosmin-1, a secreted protein present in various extra-cellular matrices during the organogenesis period. The *FGFR1* gene, which codes for a FGF (*fibroblast growth factor*) receptor, is one of the genes involved in the autosomal dominant form (KAL-2). Only a small proportion (approx. 20%) of individuals affected by this syndrome carry a mutation on either the *KAL-1* or *FGFR1* gene. The mutations identified lead to functional loss of the corresponding protein. Several other genes are to be discovered.

Diagnostic methods

Laboratory tests: they consist of hormones evaluation (GnRH stimulation test), and qualitative and quantitative olfactometric evaluation.

Genetic counseling

It must be adapted to each family, taking into account the high variability of clinical expression, even within a family.

Prenatal diagnosis

It is not relevant.

Unresolved questions and comments

- Discovery of other genes responsible for the autosomal forms
- Does the autosomal recessive form really exist (or is it in all the non X-linked cases a dominant form with variable penetrance)?
- Taking into account the relative rarity of the X-linked cases (KAL-1), how can the marked male predominance of the disease be explained? Possible role of the physiological inequality of dosage of the *KAL-1* gene product between the two sexes (*KAL-1* partially escapes inactivation in women).
- Correlations between genetic forms and clinical symptomatology (associated clinical signs in particular)
- Causes of the phenotypic variability, including within a family (modifying genes?)

References

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