Reminder of important clinical lesson

Kallmann syndrome in a female adolescent: a new mutation in the FGFR1 gene

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Summary

The Kallmann syndrome is characterised by the association of hypogonadotropic hypogonadism and hypo/anosmia. It represents a phenotypically and genotypically heterogeneous clinical entity, with six genes identified so far in the literature—KAL1, FGFR1, PROKR2, PROK2, CHD7 and FGF8. Mutations in the FGFR1 gene can be found in approximately 10% of the patients. The authors present the case of a female adolescent with hypogonadotropic hypogonadism and impaired olfactory acuity in the presence of hypoplasia of the nasal sulcus and agenesis of the olfactory bulbs. The molecular analysis of the fibroblast growth factor receptor 1 identified a heterozygous mutation c.1377_78insA (p.V460SfsX3) in exon 10 of FGFR1 gene. This mutation has not yet been reported in the literature. A theoretical review of clinical features and therapeutic approach of this syndrome is also presented.

BACKGROUND

The Kallmann syndrome (KS) is a rare clinical entity, with an estimated prevalence of 1:8000 in males and 1:40 000 in females,^{1 2} characterised by the association of hypogonadotropic hypogonadism and hypo/anosmia.^{1 3}

The first description of this syndrome was attributed to the Spanish anatomist Aureliano Maestre de San Juan, who, in 1856, reported the absence of cerebral olfactory structures in a patient with small testicles, micropenis, absence of pubic air and anosmia. However, it was not until the next century (1944) that this syndrome was recognised as a clinical entity by the American geneticist Franz Josef Kallmann, who, while studying the presence of hypogonadism and anosmia in three distinct families, proved its inherited trait.^{1 4}

Considering the pathophysiological point of view, KS results from an embryogenic defect. The impaired olfactory acuity occurs as a consequence of a unilateral or bilateral hypoplasia/agenesis of the olfactory system. Embryologically, the gonadotropin-releasing hormone (GnRH) neurons derive from the olfactory placodium and migrate to the hypothalamus through the olfactory beam. The normal development of the olfactory bulb is therefore an absolute condition to an adequate migration of the GnRH neurons to the hypothalamus, which explains the involvement of the gonadotropic axis observed in this syndrome.^{3 5}

The KS may occur in both sporadic and inherited forms. As the majority of cases are sporadic, a high frequency of de novo mutations in the genes involved is suggested.

In the inherited form, the transmission is autosomal recessive, autosomal dominant with incomplete penetration or X linked.^{1 2}

Until present, six causal genes have been identified—KAL1, FGFR1, PROKR2, PROK2, CHD7 and FGF8—and

KS is classified according to this into six different subtypes, from KAL1 to KAL6, respectively.^{1 2 6}

Until now, the finding of KAL1 mutations in male patients with KS has demonstrated that this gene is responsible for the X linked recessive form of the disease.²

Mutations in these six genes are observed in only 30% of all patients with KS, suggesting a possible involvement of other genes in its aetiology.^{1 2}

CASE PRESENTATION

The authors report the case of a Caucasian female adolescent, referred to the Paediatric Outpatient Clinic at 11 years of age because of short stature.

She was the only child of young, healthy and non-consanguineous parents. No family history of pubertal delay or known inherited familial diseases was reported.

Pregnancy, birth and neonatal period had occurred uneventfully. Anthropometry at birth was adequate for gestational age. From the second year of life, a linear growth (both weight and stature) below percentile 3 was observed. She also presented adequate neurodevelopment skills.

At first evaluation (11 years of age) she had a good general appearance, weighed 26 kg and was 127 cm tall (SD score (SDS) −2.56; percentile <1); her body mass index was of 16.1 kg/m² (SDS −0.82; percentile 20.5) and she was prepubertal. Physical examination was otherwise normal, with no dysmorphic features or malformations.

The target height was 154.5 cm (SDS −1.25; percentile 10.5) and growth velocity during the previous year had been normal.

INVESTIGATIONS

The initial laboratory workup revealed a normal hormonal basal study according to age, sex and Tanner stage

(follicle-stimulating hormone (FSH), luteinising hormone (LH) and thyroid function), IGF 1 within normal range value (262 µg/l), a female karyotype (46, XX), negative antitransglutaminase IgA antibodies and a bone age of 10 years.

Blood count, extended biochemistry, serum IgA levels, erythrocyte sedimentation rate and urinalysis were all within the normal range; microbiological examination of the urine and parasitological examination of faeces were negative.

Follow-up was carried out in an outpatient care department and 2 years later, at the age of 13 years and 6 months, she was still prepubertal. Hormonal study was repeated at this point revealing low values of FSH, LH and oestradiol for sex and chronological age.

An luteinizing hormone-releasing hormone (LHRH) stimulation test was performed demonstrating a prepubertal LH response. The remaining pituitary function was normal. The abdominal and pelvic ultrasonography also revealed prepubertal uterine dimensions, with no anomalies detected.

The review of the anamnesis was able to identify anosmia.

Considering the clinical association of hypogonadotropic hypogonadism and anosmia, an encephalic and pituitary MRI was performed, which showed a hypoplasia of the nasal sulcus and bilateral agenesis of the olfactory bulbs.

The molecular analysis of the fibroblast growth factor receptor 1 (FGFR1), by sequence analysis of all coding region (exons 2–18), and including the adjacent intronic regions, allowed the identification of the mutation c.1377_78insA (p.V460SfsX3) in heterozygous on exon 10.

TREATMENT

At the age of 14, treatment with transdermal oestradiol was started, beginning with an initial dose of 6.25 µg/day, and gradually increasing to a maximum dose of 25 µg/day. Three months after this therapeutic approach she began her pubertal development.

OUTCOME AND FOLLOW-UP

At the age of 17, her height was 149.5 cm (SDS –2.11; percentile 1.77), her body mass index was of 20.27 kg/m² (SDS –0.29; percentile 38.64) and she was on a Tanner stage 3 with normal uterine dimensions for chronological age. A progestative was introduced and, 1 month later, a withdrawal haemorrhage occurred.

At present, at the age of 18, her height is 151 cm (SDS –1.84; percentile 3.3) with a body mass index of 20.74 kg/m² (percentile 43.59).

DISCUSSION

In the case reported, the presence of hypogonadotropic hypogonadism in association with olfactory impairment and hypoplasia/agenesis of the encephalic olfactory structures, allowed the clinical diagnosis of KS. The molecular identification of a new mutation on the FGFR1 gene corroborated it.

Clinically, the KS is mainly characterised by absence or incomplete puberty in the presence of hypogonadotropic hypogonadism with hypo/anosmia. Patients rarely value the latter sign during the clinical history, which

emphasises the importance of its exclusion when a hypogonadotropic hypogonadism is suspected.²

This also happened in our patient who did not spontaneously mention the presence of an olfactory impairment.

KS is a heterogenic entity. The degree of olfactory and hypogonadism can substantially vary, among unrelated patients and within the same family or even between monozygotic twins.¹

A subgroup of patients with KS can present other clinical manifestations, such as: bimanual synkinesis, abnormal ocular movements, congenital ptosis, coloboma of the iris, nasal cartilage agenesis, malformation of the external ear, cleft lip or palate, unilateral or bilateral renal agenesis, agenesis of the corpus callosum, hypodontia, skeletal anomalies of the feet and hands, obesity and sleep disorders.^{1 2 5}

In the reported case, none of these associated signs and symptoms was present.

The sequencing analysis of the FGFR1 gene allowed the identification of a c.1377_78insA (p.V460SfsX3) mutation in heterozygous state located on exon 10. This c.1377_78insA mutation causes a frameshift starting with codon Val460 changing it to serine and creates a premature stop codon at position 3 of the new reading frame, denoted (p.V460SfsX3).

Although the mutation identified in this case has not yet been published in the literature or inserted on the Human Gene Mutation Database Professional, it can be regarded as pathogenic since protein function is compromised, being consistent with the diagnosis of KS 2 (OMIM #147950).

According to Dodé and Hardelin,¹ mutations in the FGFR1 gene are present in about 10% of all cases of KS, corresponding, in 30% of those cases, to de novo mutations.

Our patient seems to represent one of such cases, since, from the clinical point of view, the family history was negative. Nevertheless, considering the wide intrafamilial phenotypic variability, only an FGFR1 gene molecular analysis performed on each family member would allow a definitive conclusion on the supposed occurrence of a de novo mutation in this case.

The therapeutic approach of the KS is based on the management of hypogonadism, promoting the development of secondary sexual characteristics as a primary goal and, secondarily, fertility.^{1 2}

Similar to other causes of hypogonadism, a chemical induction of puberty is required, through the administration of sexual steroids.^{1 2}

On the female sex, the hormone replacement therapy with oestrogens should be gradual, beginning with low doses of oestrogens, to mimic, as much as possible, physiological puberty. Concerning the route of oestrogen administration, transdermal application seems to be a more physiological alternative, when compared with oral administration.

Initial treatment includes the administration of a low dose of oestrogens, approximately 6.25 µg/day if transdermal, with a progressive dose increase during a period of 2 years. The progestative should be associated only when withdrawal haemorrhage occurs or otherwise not until 2 years after the introduction of oestrogens, in a way to provide adequate breast and uterine development.⁷ This last approach was the one chosen for our patient.

To induce ovulation in females and enhance the production of spermatozooids in men, gonadotropins may be used, as well as a pulsatile administration of GnRH. Both approaches are effective in the vast majority of patients.^{1 2}

Although previously thought to be a lifelong disorder, some cases of reversible KS may occur, characterised by the existence of fertility in the absence of treatment with GnRH or gonadotropins and/or by the improvement in testosterone secretion after discontinuation of treatment with gonadotropins, GnRH or testosterone replacement.³

Those cases were all reported in males,^{3 8} and therefore it is not expected that such a situation would occur in our female patient.

Learning points

- ▶ In patients with suspected hypogonadotropic hypogonadism it is important to value the presence of other clinical signs such as hypo/anosmia.
- ▶ Genetic testing strategy in Kallmann syndrome is based on patient gender and family history (if any), the supposed mode of disease inheritance, as well as the presence of additional clinical anomalies.
- ▶ Since up to 30% of the mutations found in the FGFR1 gene might be de novo mutations, this possibility should be considered when assessing recurrence risk of this genetic form in a family.

Competing interests None.

Patient consent Obtained.

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