

CASE REPORT

Clinical, diagnostic, and therapeutic aspects of Kallmann syndrome with an *FGFR1* gene variant in a female adolescent

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ABSTRACT

This report details a case of a female patient with genetically confirmed Kallmann syndrome, which was found to be related to a novel molecular variant of the *FGFR1* gene. We present a case of a 12-year-old girl, referred to the Pediatric and Adolescent Gynecology Clinic with anosmia and the onset of puberty. The magnetic resonance imaging revealed hypoplasia of the olfactory bulbs, and initial hormonal tests confirmed her prepubertal status, but the first genetic test was inconclusive. The girl's pubertal development had an atypical course. After some time of observation, we performed a long luteinizing hormone-releasing hormone test which gave a pubertal response. The second genetic test revealed an *FGFR1* gene mutation: the new molecular variant c.2187-2A>G,p. Estroprogestin therapy was administered with good clinical results. Early detection of Kallmann syndrome allows timely initiation of puberty-inducing treatment, resulting in normal physical and psychosocial development. Genetic confirmation of the syndrome, although rare, seems to be relevant for family planning of patients and early diagnosis in their offspring.

KEY WORDS:

puberty, *FGFR1*, Kallmann syndrome, amenorrhea, hypogonadotropic hypogonadism.

INTRODUCTION

Kallmann syndrome is a rare genetic disorder, which refers to the association between hypogonadotropic hypogonadism and anosmia or hyposmia due to abnormal migration of olfactory axons and gonadotropin-releasing hormone producing neurons. This report details a case of a female patient with genetically confirmed Kallmann syndrome, which was found to be related to a novel molecular variant of the *FGFR1* gene.

CASE REPORT

The 12-year-old girl was referred to the Pediatric and Adolescent Gynecology Clinic with anosmia and the onset of puberty. The child was born naturally, from her mother's third physiological pregnancy, in week 39 of gestation. In

early childhood she was diagnosed with anosmia. The magnetic resonance imaging (MRI) scan results showed that her olfactory bulbs were barely noticeable, concluding that it may correspond to olfactory bulb hypoplasia. There were no other visible changes within the patient's brain, nor was there any extension in the ventricular system. During the patient's first gynecological consultation (height 147.3 cm; weight 37 kg) the assessment of her sexual development based on the Tanner score was performed: Th II/III, Pb I. A transabdominal ultrasound revealed that she had a prepubertal uterus and ovaries (Table 1). The patient's hormonal status was also prepubertal (Table 2).

A next-generation sequencing 1000 panel (NGS) genetic test neither confirmed nor excluded the presence of Kallmann syndrome. During the next 10 months, the patient exhibited only mild signs of puberty. We performed hormonal tests, including a luteinizing hor-

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TABLE 1. Transabdominal ultrasound results

Patient's age [years]	Uterus length [mm]	Uterus height (AP) [mm]	Endometrium [mm]	Cervix length [mm]	Volume of ovaries [ml]
12	23	6	Not visible	22	1.8, 2.0
14	25	13.5	1.8	22	1.8, 2.15
14.5	33	19.5	2.0	24	Each 3.4

AP – antero-posterior diameter

TABLE 2. Initial hormonal assay

Initial hormonal assay	Patient's values	Normal values
FSH [IU/l]	2.9	0.4–12.7
LH [IU/l]	0.6	0–0.9
Estradiol [pg/ml]	< 8.0	25–100
Prolactin [ng/ml]	8.22	2.7–19.7
TSH [μ U/ml]	1.92	0.4–4.0
FT3 [pg/ml]	3.23	1.5–4.0
FT4 [ng/dl]	1.11	0.8–1.8
Cortisol [μ g/dl]	7:30 – 22.9, 8:00 – 20.0	7–25

FSH – follicle stimulating hormone, FT – thyroxine, LH – luteinizing hormone, TSH – thyroid stimulating hormone

mone-releasing hormone (LHRH) test, and received a weak pubertal response (Table 3).

The next gynecological consultation was conducted when the patient was 13 years and 9 months old (height 156 cm, weight 44.4 kg). We did not observe any progression in sexual development or on ultrasound examination. Thus, we decided to introduce estradiol orally (0.5 mg/day). Three months later, improvement was visible only on gynecological ultrasound (Table 1). The dose of estradiol was increased to 1 mg/day, and 5 months later enlargement of the breasts (Th III) and uterus (length 28 mm, antero-posterior diameter 18 mm, endometrium 2.5 mm) was noticeable. We continued the therapy. When the patient reached the age of 14.5, she still did not begin to menstruate, but we observed changes in the gynecological ultrasound results (Table 1). The next few months were a plateau. The girl was now 15 years old, and was 163.9 cm tall, with normal secondary sexual characteristics. Nevertheless, in spite of estradiol therapy, the patient still did not begin menstruating, and the gynecological ultrasound was comparable with the previous one. We then decided to stop estradiol therapy and to perform hormonal tests, which showed: follicle-stimulating hormone

TABLE 3. Second hormonal assay with luteinizing hormone-releasing hormone test

Second hormonal assay	Patient's result in 0 min	Patient's result after 60 min
FSH [IU/l]	4.23	8.35
LH [IU/l]	1.48	10.7
Estradiol [pg/ml]	< 8.0	–
TSH [μ U/l]	2.997	–
FT3 [pg/ml]	3.61	–
FT4 [ng/dl]	1.06	–

FSH – follicle stimulating hormone, FT – thyroxine, LH – luteinizing hormone, TSH – thyroid stimulating hormone

(FSH) – 1.62 IU/l (0.4–12.7 IU/l), luteinizing hormone (LH) – 1.45 IU/l (0–0.9 IU/l), estradiol – < 8.0 pg/ml (25–100 pg/ml), prolactin – 5.26 ng/ml (2.7–19.7 ng/ml). For the next 3–4 months the girl reported an improvement in her sense of smell, but she still did not menstruate. The patient's mother had her menarche at the age of 13. We performed a long LHRH test (the girl was 15.5 years old at the time) and received a pubertal response (Table 4).

Once again, genetic testing was performed using NGS, as the genetic laboratory had a new panel that allowed for a broader diagnosis of Kallmann syndrome. It turned out that the patient was a heterozygous carrier of the variant in the *FGFR1* gene (c.2187–2A>G,p). This variant has yet to be reported in the literature or included into the Human Gene Mutation Database Professional. Given that protein function is impaired, and the clinical features presented by our patient are consistent with a diagnosis of Kallmann syndrome, we consider it to be a pathogenic one. Verification of this result with traditional Sanger sequencing as well as genetic tests on her parents were later ordered. The girl's diagnosis was confirmed and the test results ruled out Kallmann syndrome in both of her parents. Later on, the patient was 16 years old (height 165 cm, weight 46.6 kg) and still had not begun to menstruate. However, an ultrasound examination

TABLE 4. Long luteinizing hormone-releasing hormone test

Hormonal assay	0 min	30 min	60 min	90 min	120 min
FSH [IU/l]	6.04	14	15.4	15.3	17.1
LH [IU/l]	2.09	34.5	34.5	26.4	24.8

FSH – follicle stimulating hormone, LH – luteinizing hormone

revealed an increase of endometrial thickness (3.7 mm) and volume of ovaries (4.5 ml). We performed a progesterone challenge test using lynestrenol orally (5 mg/day), which was positive. For the next 6 months the girl did not have any menstruation. We introduced hormonal therapy with estradiol (1 mg/day) and lynestrenol (5 mg/day) orally as of the 12th day of her cycle. Currently, the patient has regular menses without any complaints.

DISCUSSION

Kallmann syndrome is a condition defined by delayed or absent puberty and an impaired sense of smell (anosmia or hyposmia). The syndrome results from the aberrant migration of neurons that were destined to differentiate into the olfactory bulbs or gonadotropin-releasing hormone (GnRH)-secreting cells. A deficiency in the production and secretion of the GnRH neurohormone results in a reduction in gonadal activity. Kallmann syndrome represents one of the most common causes of congenital hypogonadotropic hypogonadism. It is estimated that Kallmann syndrome is five times more prevalent in males than in females, with an incidence rate of 1 : 50,000 in the latter. According to the literature, there have been identified over 30 genes that correlate with Kallmann syndrome (e.g. *FGFR1*, *FGF8*, *CHD7*, *SOX10*). It can be inherited in an autosomal dominant or recessive manner, or can be linked with the X chromosome.

Kallmann syndrome is characterized mainly by hypogonadotropic hypogonadism, which clinically manifests as the absence of or delayed puberty, and olfactory disorder. Moreover, some concomitant dysfunctions have also been reported, including: hearing impairment, cleft lip and/or palate, dental agenesis, and kidney and heart defects. Out of all the described comorbidities, our patient presented only anosmia. Her case showed some breast development, but the puberty process progressed slowly, with periods of inhibition.

A genetic test confirmed the diagnosis and revealed a new variant within the *FGFR1* gene (c.2187–2A>G,p). *FGFR1* belongs to the tyrosine kinase superfamily of receptors, which enables signaling through the mitogen-activated protein kinase pathway. This mode of communication is of vital importance for the migration, differentiation, and survival of neurons, as well as for cell proliferation during the embryonic developmental process [1].

The symptoms are sex and age dependent, and diagnosis is much easier in boys. Cases within girls pose a diagnostic problem during infancy and childhood, as these are periods of physiological hypogonadism. Genetic testing is of particular importance in the diagnostic process for female offspring of parents with Kallmann syndrome [2]. It should also be stressed that the suspicion of Kallmann syndrome usually arises too late (older adolescents or young adults). The majority of patients diagnosed with Kallmann syndrome do not experience the onset of pu-

berty. In some cases, the process of puberty may cease prematurely. The key symptom among female patients is the absence of breast development and primary amenorrhea [3]. Due to the fact that our patient was admitted to us on time, we were able to start conducting tests and treatment. We did not observe any serious anomalies in the girl's growth and development process. However, we should also remember about young adults with Kallmann syndrome, who report to a physician due to fertility problems or osteoporotic fractures resulting from sex hormone deficiency. Therefore, early diagnosis and treatment are extremely important, as this is the most effective way to ensure the best possible outcome for the patient.

A comprehensive physical examination, with a particular emphasis on estrogenization, is of paramount importance [4]. Under these circumstances, a biochemical evaluation includes a variety of tests, such as FSH, LH, and estradiol, but also thyroid stimulating hormone, thyroxine prolactin and cortisol levels to exclude other causes of hypogonadotropic hypogonadism (e.g. a pituitary tumor). Generally, hypogonadotropic hypogonadism patient gonadotropin levels are low or normal, while their estradiol level is low or sometimes indeterminable. It is well established that serum levels of estradiol are correlated with the development of the breasts. In the majority of cases where breast development is absent, the levels of estradiol are either markedly low or undetectable. Serum levels of estradiol are usually measurable in women with breast development beyond Tanner stage II. The outcome of a GnRH stimulation test seldom permits the distinction between a constitutional delay of growth and puberty and Kallmann syndrome [5]. Furthermore, the diagnostic process should include cranial MRI to exclude brain tumors and assess olfactory structures. Gynecological ultrasonography seems to be essential in this matter, as it enables the assessment of ovaries and the patient's uterus. Kallmann syndrome diagnosis is mainly based on clinical features. Pathogenic variants in more than 25 genes account for about half of all individuals with isolated GnRH deficiency (IGD). Approximately 60% of patients with IGD have an impaired sense of smell. To confirm changes in genes linked to Kallmann syndrome, Sanger sequencing is the gold standard for authenticating nucleotide alterations identified through NGS. Performing genetic testing is very helpful for the diagnosis, prognosis and genetic counselling [6]. A significant area of interest among patients with Kallmann syndrome and their parents is the potential risk of transmitting the disease to their offspring. It is of the utmost importance that male individuals diagnosed with X-linked Kallmann syndrome be informed of the automatic transmission of the gene variant to their unborn daughters, who will be definite carriers. Moreover, genetic counseling for these girls should be initiated following the onset of puberty.

The therapeutic management of the patient is contingent upon their age and their expectations regarding

fertility, as these factors influence the most appropriate course of treatment. There is no cure for anosmia. The primary objective of the therapeutic intervention is to stimulate the estrogenization process and restore normal sexual function. Additionally, it aims to promote growth, enhance bone health, address concerns regarding future fertility, and improve psychological and emotional well-being [7]. Puberty can be induced by a low dose of estradiol (oral or transdermal) exclusively to promote breast development. After the patient's first period or after 12–24 months of estrogen treatment, gestagen should be added. The implementation of estrogen-progestin therapy has been demonstrated to facilitate the normal development of the breasts and genitals, which is also of particular significance with respect to the formation of a sense of femininity. Estrogen therapy allows normal uterine size to be achieved and, when combined with progestins, causes regular withdrawal bleeding.

CONCLUSIONS

The diagnosis of congenital hypogonadotropic hypogonadism in girls is a challenge. The absence of or a decreased sense of smell allows us to suspect Kallmann syndrome. Careful observation, several hormonal tests, gynecological ultrasound and genetic counselling are also of great value in such situations. Early diagnosis enables the implementation of puberty inducing treatment on time and resulting in normal psychosocial development as well as the possibility of having offspring. Genetic confirmation also seems to be an important factor in determining whether the Kallmann syndrome patient's future offspring will have it or not.

DISCLOSURES

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