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Diagnosis and treatment of Kallmann syndrome in women – a challenge for the endocrinologist

Rozpoznanie i leczenie zespołu Kallmanna u kobiet – wyzwaniem dla endokrynologów

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Summary

Kallmann syndrome is one of the most common causes of congenital hypogonadotropic hypogonadism caused by deficient production of gonadotropin-releasing hormone (GnRH). The disorder is characterised by an absence of puberty, infertility and defective sense of smell. Congenital hypogonadotropic hypogonadism can be associated with other developmental anomalies such us cleft palate, renal agenesis, skeletal and heart anomalies. Kallmann syndrome can be challenging to diagnose in adolescent and young adult women, especially when attempting to differentiate it from constitutional delay of growth and puberty. Diagnosis is based on hormonal analysis of gonadotropins, sex hormones, anti-Müllerian hormone (AMH) and inhibin B. Genetic confirmation is obtained only in 20-30% cases. The essence of treatment is induction of puberty and fertility.

Streszczenie

Zespół Kallmanna jest jedną z najczęstszych przyczyn wrodzonego hipogonadyzmu hipogonadotropowego będącego następstwem deficytu wydzielania neurohormonu GnRH. Charakteryzują go: opóźnienie dojrzewania, niepłodność oraz brak lub osłabienie węchu. Ponadto mogą współistnieć inne zaburzenia rozwojowe (np. rozszczep podniebienia, wady nerek, serca, układu kostnego). Rozpoznanie zespołu Kallmanna jest wyzwaniem u nastolatek i młodych dorosłych kobiet, szczególnie trudne jest różnicowanie z konstytucjonalnie opóźnionym wzrastaniem i dojrzewaniem. Diagnostyka opiera się głównie na oznaczeniu stężenia: gonadotropin, hormonów płciowych, hormonu antymüllerowskiego (AMH) oraz inhibiny B. Genetyczne uwarunkowanie udaje się potwierdzić jedynie w 20-30% przypadków. Istotą leczenia jest indukcja pokwitania oraz zwiększenie szans na posiadanie potomstwa.

INTRODUCTION

Kallmann syndrome, one of the most common causes of congenital hypogonadotropic hypogonadism (accounting for approximately 50% of cases) is the result of deficient production and secretion of the GnRH neurohormone leading to a decreased activity of the gonads. The majority of patients also suffer from the lack or severe dysfunction of the sense of smell (hyposmia or anosmia). Kallmann syndrome is the result of abnormal development of GnRH neurons. During organogenesis of the hypothalamus and olfactory bulbs the migration of neurons differentiating into the olfactory bulb or GnRH-secreting cells is disordered (1, 2).

The prevalence of Kallmann syndrome is estimated to be 1: 10,000 in boys and very low, 1: 50,000 in girls (1). Kallmann syndrome is difficult to diagnose in girls in early life due to a significant variety of clinical, hormonal and genetic symptoms. The syndrome is usually diagnosed in adolescent girls or only in adulthood due to the difficulty in differentiating Kallmann syndrome from other causes of delayed puberty or absence thereof.

Classic Kallmann syndrome is inherited in an X-linked autosomal dominant pattern (mutation of the KAL 1 gene); however, autosomal recessive inheritance has also been confirmed. In addition, the rare occurrence of this syndrome has been reported (1, 2). According

to the literature over 25 different genes correlated with Kallmann syndrome have been identified (FGFR1, FGF8, CHD7, SOX10) (2). A genetic link has been confirmed in only 20-30% of cases (3).

Main components of Kallmann syndrome in adolescent girls and young adult women:

1. Congenital hypogonadotropic hypogonadism, absence of or a decreased sense of smell in the majority of affected individuals, disordered secretion of gonadotropins and sex hormones by the gonads, clinical absence of or delayed puberty, no signs of puberty in girls after 13 years of age (child-like proportions of the body, absence of breast development – Tanner stage I).
2. Other concomitant dysfunctions:

– hearing impairment,
– cleft lip and/or palate, dental agenesis,
– kidney and heart defects,
– skeletal system anomalies,
– eunuchoid body proportions,
– malocclusion/gothic palate (1-5).

CASE REPORT

A 23-year-old woman was admitted to the Department of Endocrinology of the Centre of Postgraduate Medical Education (CKMP) in order to determine the cause of primary amenorrhoea. The patient had been under the care of a paediatric endocrinology ward and clinic by 19 years of age. She was born from a normal full-term pregnancy with normal body mass and length. She had a normal psychomotor development, although a severely decreased sense of smell was observed already in early childhood. At 14 years of age symptoms of adrenarche appeared, small acne lesions appeared on the face and pubic and axillary hair developed, without other signs of puberty. Olfactory dysfunction was found in the patient's grandmother and brother. Hearing impairment was also diagnosed in the brother. Due to the lack of menses endocrinological assessment was conducted at 16 years of age. It revealed child-like body proportions, absence of breast development (Tanner stage I), the presence of axillary and pubic hair as well as normal body mass and height. Hormone tests demonstrated a very low estradiol level – 8.93 pg/ml and low levels of gonadotropins: FSH – 4.15 IU/l, LH – 2.56 IU/l. In an LHRH test an increase of the LH level from 2.31 up to 36.0 IU/l in 30 minutes and an increase of the FSH level from 3.52 up to 10.6 IU/l in 90 minutes were observed.

Delayed puberty was diagnosed and hormone replacement therapy was introduced (Estrofem, Estrofem mite). During the treatment regular menses occurred. Breast development took place around 19 years of age after 3 years of treatment. Hormone replacement therapy was discontinued after 6 years in 2015. No menstrual bleeding has appeared since then.

The patient reported to the Department of Endocrinology of the Centre of Postgraduate Medical Education at 23 years of age (August 2016) in order to determine the cause of primary amenorrhoea. The last menstruation after HRT occurred in October 2015. Physical examination revealed a normal, female physique, normal body mass and height, BMI of 20.1 kg/m^2, normal pubic and axillary hair, normal breast structure (normal glandular tissue was observed in an ultrasound examination). Gynaecological examination demonstrated a normal structure of the reproductive organ.

Hormone tests revealed:

– low level of estradiol – 18.8 pg/ml (day 257 of cycle),
– no increase in FSH (8.2 IU/l) or LH (5.5 IU/l),
– despite oestrogen deficiency,
– normal levels of testosterone, androstenedione, prolactin, TSH, fT4, cortisol, DHEA-S, 17-hydoxyprogesterone and IGF-1,
– MRI examination of the hypothalamic-pituitary system and the brain: pituitary gland unenlarged, with no distinct focal lesions. Pituitary stalk positioned along the axis, unchanged. Posterior pituitary lobe with a normal signal. Cavernous sinuses, suprasellar cisterns with the optic chiasm, hypothalamic structures and olfactory bulbs unchanged. Normal brain tissue and intracranial fluid spaces,
– ultrasound examination of the reproductive organ: endometrial thickness 5 mm (day 257 of cycle), relatively small ovaries: right – 3.42 cm^3, left – 3.76 cm^3, both with a normal echostructure,
– anti-Müllerian hormone level (AMH): 4.45 ng/ml (healthy women control group values: 3.85 ± 0.68 ng/ml – own research),
– normal image of the heart in echocardiography,
– normal abdominal organs in ultrasound,
– basic tests did not reveal significant abnormalities; haemochromatosis was excluded among other conditions.

Based on the overall clinical picture Kallmann syndrome was diagnosed. It is probably familial in nature; genetic tests of the patient and her brother are still being processed. Hormone replacement therapy was prescribed.

DISCUSSION

Kallmann syndrome is a rare disease which is difficult to diagnose, especially in girls in early life. The characteristic components of the syndrome include hypogonadotropic hypogonadism and olfactory dysfunction.

The symptoms are age- and sex-dependent. Cryptorchidism with the frequently accompanying micropenis suggests congenital hypogonadotropic hypogonadism (1-3, 5). In such cases gonadotropins, sex hormones and inhibin B tests allow for the establishment of a diagnosis already at 1-2 months of age. This period is asymptomatic in girls. It is only in the offspring of parents with Kallmann syndrome that early diagnosis is possible based on a low level of FSH (absence of mini-puberty) and the lack of response to GnRH (6).

It needs to be emphasised that the suspicion of Kallmann syndrome usually arises too late, as in the case of our patient. It usually takes place in older adolescents or young adults due to delayed puberty defined

in boys as the lack of signs of puberty after 14 years of age and in girls after 13 years of age.

In the majority of patients with Kallmann syndrome there is no onset of puberty or, less commonly, the process of puberty stops. Both in boys and in girls no growth acceleration or changes in body structure are observed. The key symptom in girls is the absence of breast development and primary amenorrhoea, as in our patient (7, 8). Boys report to a physician due to a decreased libido, sexual dysfunction and the absence of virilisation. The characteristic features revealed in physical examination include low testicular volume < 4 ml and eunuchoid body proportions (7, 8). Young adults present with fertility disorders and osteoporotic fractures as a result of sex hormones deficiency. For this reason, early diagnosis and treatment are so important.

The diagnosis of the Kallmann syndrome is primarily based on hormone tests such as sex hormones, gonadotropins, inhibin B and anti-Müllerian hormone levels. In boys with isolated hypogonadotropic hypogonadism a low level of testosterone (usually < 2 nmol/l) with accompanying low or normal gonadotropin levels is a typical sign; similarly in girls – a low or sometimes indeterminable estradiol level is accompanied by low or normal FSH and LH levels. It is suggested that basal gonadotropin tests have a higher diagnostic value that GnRH stimulation tests (9).

The result of a GnRH stimulation test rarely allows for the differentiation between constitutional delay of growth and puberty and Kallmann syndrome (9). Determining inhibin B and AMH levels is helpful (9). In Kallmann syndrome in boys the AMH level is decreased, while in adolescent girls and young adult women the AMH level is usually within normal limits. In addition, in the majority of cases olfactory dysfunction and positive medical history for Kallmann syndrome are found.

Genetic testing, although not easily available in Poland, is very important and helpful for the diagnosis, prognosis and genetic counselling (10).

Therapeutic management of the patient depends on the age and expectations regarding fertility. In male infants orchidopexy is recommended at 6-12 months of age and in the case of a micropenis treatment with low-dose testosterone is recommended (11, 12).

In adolescents and young adults the aim of the treatment is virilisation in boys and oestrogenisation in girls, improvement in sexual function and consequently, growth increase, rise in bone mineral density and improvement of chances of having offspring (13, 14).

Treatment usually begins with hormone replacement. Low-dose testosterone is used in boys with a gradual increase up to the adult dose (15).

In girls it is very important to start treatment with low-dose estradiol exclusively (0.1 mg daily) for 12-24 months for optimal breast development. Subsequently gestagen should be added (16). In order to achieve fertility human chorionic gonadotropin with menopausal gonadotropin (HMG) or sometimes human recombinant FSH is used. The optimal solution would be subcutaneous administration of GnRH using a personal pump; however, due to the high cost it is not possible in Polish conditions.

The diagnosis of congenital hypogonadotropic hypogonadism is a challenge, especially during puberty due to the difficulties in differentiating it from constitutional delay of growth and puberty. The absence of or a decreased sense of smell and determining gonadotropin, sex hormones, inhibin B and AMH levels are helpful, but do not always allow for establishing a diagnosis with certainty. Further research is necessary on new biomarkers facilitating the differentiation between the two conditions. It is worth stressing the fact that the essence of effective treatment of Kallmann syndrome is not only the induction of puberty, but also increasing the chances of having offspring.

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