

Conference Paper

Kallmann Syndrome: A Case Report

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Abstract

A 32 yr old woman came to the hospital with a history of treatment for primary amenorrhea once in 2007. Diagnosis of Kallmann syndrome was made based on her complaint of amenorrhea and anosmia. Physical examination revealed abnormal growth of secondary sexual characteristic including undeveloped breasts, lack of armpit and pubic hair. The external genitalia examination showed very slightly pubic hair, a small labia minora, and vagina (\pm 0.5 cm diameter, 5 cm depth). The abdominal ultrasound examination showed a small uterus. Bone marrow densitometry examination denoted osteoporosis in L1, L2, L3, L4 vertebrae and pelvic bone. Chromosomal examination showed the karyotype of 46 XX. The olfactory test resulted in anosmia. Kallmann syndrome is a developmental disorder which consists of a combination of hypogonadotropic-hypogonadism and anosmia. The characteristics of patients diagnosed with Kallmann syndrome were delayed puberty and anosmia. A chromosomal and hormonal examination might be performed to rule out Klinefelter and Turner syndrome. Magnetic Resonance Imaging (MRI) examination was useful to determine whether there was any olfactory bulb or pituitary gland and hypothalamus disorder. Patient's management included hormone replacement therapy and fertility therapy to maintain healthy hormone circulation equal to a normal physiological value according to patients' ages. In this case, the effect of the drugs was to build a temporary endometrial wall. Once the pills are stopped, the patient will not undergo her menstruation phase anymore because of her pituitary hormone production is inadequate. This medication also gave more strength to bones due to her osteoporosis.

Keywords: Amenorrhea, Anosmia, Genetic disorder, Hypogonadism-hypogonadotropic, Kallmann syndrome.

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1. Introduction

Kallmann Syndrome is a developmental disorder combined with hypogonadotropic-hypogonadism and anosmia or hyposmia, where the individual's olfactory function is decreased [1]. This anosmia or hyposmia is related to the lack of bulb or olfactory tract hypoplasia. This hypogonadism is caused by a deficiency of gonadotropin-releasing hormone (GnRH) and is a result of the failure of synthetic embryonic migration of gonadotropin-releasing hormone neurons to the forebrain [2, 3].

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The correlation between anosmia and reproduction system disorder was first presented by a Spanish pathologist named Maestre de San Juan in 1856. He did not discover any olfactory bulb in male cadavers who had anosmia in their lives. A geneticist from America in 1944 named Franz Josef Kallmann published a study related to the genetic explanation on the condition of patients with sexual immaturity and anosmia and presented it as a syndrome. This syndrome is defined as a combination of signs and symptoms which can cause certain diseases. Afterward, the syndrome is called Kallmann Syndrome [3, 4]

The terminology used to describe cases with Hypogonadotropic-Hypogonadism (HH) may vary. The term Congenital Hypogonadotropic-Hypogonadism (CHH) is often used today. Other terms which can be used are Idiopathic Hypogonadotropic-Hypogonadism (IHH), normosmic Hypogonadotropic-Hypogonadism (nHH) or hypothalamic hypogonadism. The term HH can be used for all cases, including Kallmann syndrome [6].

The term hypogonadism describes a low amount of sex hormone circulation; testosterone in men and estrogen and progesterone in women. Hypogonadism could happen in some different methods. The use of the term hypogonadotropic is related to hypogonadism discovered in HH which is caused by a disorder of the production of gonadotropin hormones which are released by the anterior pituitary gland, which are Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) [5, 6].

LH and FSH have direct roles in women's ovaries and men's testes. The lack of LH and FSH means early puberty that cannot start at the right time and eventually ovaries and testes were not managed to show normal fertility functions, which are the maturation and release of egg cells in women and sperm production in men [2– 4]. The underlying cause of the failure to produce LH and FSH is some disorders in the hypothalamus to release GnRH hormone which in normal condition stimulate the productions of LH and FSH. Without normal release of GnRH, pituitary gland cannot release LH and FSH, causing disorder in ovaries and testes to function normally [3, 5]. Hypogonadotropic-Hypogonadism could happen in an isolated condition which can be influenced by LH and FSH only or combination of pituitary deficiency condition as in CHARGE syndrome [7].

There are 16 genetic defects which have been described as causes of Kallmann syndrome or other forms of HH which cause disorder of GnRH production. The genes are inherited and no one with the gene defects which shows in general for all cases through the genetic test and this inheritance prediction is still debated [8]

Kallmann Syndrome is a rare disorder. The number of incidences in men is 1:10 000 and in women 1:70 000. This case report describes Kallmann syndrome in a female patient who sought treatment in Dr. Sardjito General Hospital in early 2014.

2. Case Report

A woman, 32 yr old, P0A0, came to Dr. Sardjito General Hospital with a complaint that she never had menstruation. The patient previously went to an obstetrician and gynecologist in Bumiayu (2007) and was diagnosed with hormonal deficiency and received Yasmin and Angelique pills therapy for 3 mo. The patient said there was dark red menstrual blood for 5 d. After that, there was no more menstrual blood. After consuming the medicines, the patient said her breasts became firm, and a few pubic hairs started to grow in public area. Aside from no menstruation, the patient complained that her breasts had not grown, and she did not have hair in her armpits and pubis. Another complaint from the patient is she cannot smell any scent no matter how sharp. The patient is the 11th child of 11 siblings, and the patient said no other sibling has her disorder.

The family history of high blood pressure, diabetes, asthma, heart disease, and allergy of drugs is denied. There was no history of vaginal discharge, no history of menstruation (except when she was 20 and after taking Yasmin and Angelique medicines). She had never been married and never had any sexual intercourse.

Based on physical examination in Dr. Sardjito General Hospital, it was discovered that her blood pressure was 110/70 mm Hg, pulse 86 times/min, respiration rate was 20 times/min, temperature 36.7 °C, weight 55 kg, and height 165 cm. The general condition was good, conscious, and not anemic. Examination of signs of secondary sexual growth showed undeveloped breasts with no armpit hair and very thin pubic hair. Chest and abdominal examination were within normal limit. Examination of external genitalia showed very thin pubic hair, a small labia majus and minus, clitoris and external urethral opening within normal limit. There is vestibulum of the vagina, perineal body, and mini vagina with approximately 0.5 cm diameter and 5 cm depth of sondage. A rectal examination discovered that anal sphincter muscle tonus was normal, slippery anorectal mucosa, a small uterus sized approximately (3 × 2 × 1) cm³, and a normal parametrium.

From the laboratory finding, the normal result was found in the routine blood examination. Hormonal examination result showed FSH 0.40 mIU · mL⁻¹, Estradiol < 10.00 pg · mL⁻¹, TSH 2.105 μ IU · mL⁻¹, and Prolactin 3.20 ng · mL⁻¹. During ultrasonography examination, the bladder was normal, uterus sized (4 × 1.5 × 1) cm³ was seen, and no other tumor mass was discovered. Bone marrow densitometry examination for L1, L2, L3,



Figure 1: Patient's breasts became firm after first hormonal therapy.



Figure 2: Patient's mini vagina.

L4 vertebrae and pelvic bone showed osteoporosis. Chromosomal examination showed 46, XX karyotype and the conclusion were female genotype. This patient also underwent the olfactory test and was diagnosed with anosmia.

Based on anamnesis and all of the examination, Kallmann syndrome diagnosis was given. One cycle of hormone replacement therapy with Angelique (estradiol 1 mg and drospirenone 2 mg) and Estero pills on 1 d to 21 d, the combination with Prothyra pills on 11 d to 21 d.

3. Discussion

Kallmann syndrome is a developmental disorder which consists of a combination of hypogonadotropic-hypogonadism and anosmia. The characteristics or clinical descriptions of Kallmann syndrome and hypogonadotropic-hypogonadism can be separated into two categories. It is not only reproductive, such as failure to start or reach complete puberty in men as well as women; primary amenorrhea or failure of first menstruation in women; poor growth of secondary sexual characteristics and infertility; but also non-reproductive such as hypogonadotropic-hypogonadism; anosmia or hyposmia; cranio-facial defects; unilateral agenesis or aplasia; defects in hearing nerves and teeth and synkinesis [1, 4, 9].

Not all symptoms will appear in every case of Kallmann syndrome/HH. It also does not happen to all family members. Several clinical descriptions are associated with genetic defects which are known to cause Kallmann syndrome/HH, however in several cases it is unknown why clinical descriptions of Kallmann syndrome appear. Similarly, in this case, all reproductive clinical descriptions including failure to start or reach complete puberty, primary amenorrhea, obstructed growth of secondary sexual characteristic and infertility were discovered. The discovered non-reproductive clinical descriptions included; hypogonadotropic-hypogonadism, congenital, anosmia, synkinesis, dental defect and increased height due to lateness of treatment. The cause of her Kallmann syndrome also not related to genetic disorder because based on her chromosomal examination, there is no genetic disorder. None of the patient's siblings has Kallmann syndrome like her. This could happen due to HCG which is produced by placenta in 12 wk to 20 wk of pregnancy is normally not influenced by Kallmann syndrome or HH, so nearly all patients with Kallmann syndrome and other forms of HH are born with normal sexual differentiation, physically male or female [10].

3.1. Diagnosis

Kallmann syndrome diagnosis is often made when searching for the cause of delayed puberty. One of the difficulties in diagnosing Kallmann syndrome and other forms of

HH is the ability to differentiate normal delayed puberty from Kallmann syndrome or hypogonadotropic-hypogonadism [1, 4].

Main biochemical parameters in men are low testosterone serum and low gonadotropin, LH, and FSH values and in women low estrogen serum and low LH and FSH values. In this case, laboratory examination results were $0.40 \text{ mIU} \cdot \text{mL}^{-1}$ FSH, $< 10.00 \text{ pg} \cdot \text{mL}^{-1}$ Estradiol which was lower than normal parameter.

In women and men with delayed puberty, puberty can start naturally without therapy. However, delayed therapy in cases of Kallmann syndrome/HH will cause delayed physical growth of patients and several psychological problems [4, 5]. In women, sometimes diagnosis was late because normal amenorrhea is investigated before Kallmann syndrome/HH is considered. In this case, Kallmann syndrome is established when the patient was 32 yr old because the patient had only sought treatment in Dr. Sardjito General Hospital in early 2014.

The overall endocrine examination was offered to count pituitary hormones, especially prolactin to check whether pituitary gland worked correctly. In this case, the patient's prolactin was $3.20 \text{ ng} \cdot \text{mL}^{-1}$, and this is within normal range which means that the pituitary gland worked correctly. General medical examination such as overweight or underweight due to chronic or acute diseases can cause delayed puberty. It is vital for the patients to get a complete endocrine examination to differentiate between Kallmann syndrome/HH and other cases with delayed puberty [1, 5, 12].

Bone age can be determined by X-ray examination on hand and wrist bones. If bone age is lower than the patient's age, it can be concluded as delayed puberty. BMD examination can also be performed to determine bone age, usually to spines and pelvic bones. In this case, the patient underwent BMD examination on L1, L2, L3, L4 vertebrae, pelvic bone, and was diagnosed with osteoporosis.

Chromosome examination can be performed to rule out Klinefelter syndrome and Turner syndrome, although hormonal examination can eliminate those disorders. In this case, chromosome examination was performed and showed karyotype 46, XX and the conclusion was female genotype.

Magnetic resonance imaging (MRI) examination can be used to determine whether there is any olfactory bulb and disorder in pituitary gland and hypothalamus [2, 7]. Standard olfactory examination can be used to check anosmia.

3.2. Pathophysiology

Kallmann syndrome and other forms of hypogonadotropic-hypogonadism (HH) can be categorized into pituitary and endocrine disorders. The results were puberty failure and development of secondary sexual characteristics, the cause of these disorders is between the locations of two endocrine glands in the brain [1, 4, 5].

Hypothalamus and pituitary glands control all hormonal activities in the body. The glands secrete certain amounts of various hormones with varying effects on the body. Kallmann syndrome/Hypogonadotropic-hypogonadism is produced by a communication problem between hypothalamus and pituitary on a set of hormones. Other actions of hypothalamus and pituitary glands are unaffected [1, 4, 5]. Usually, the hypothalamus releases gonadotropin-releasing hormone (GnRH). GnRH is released from hypothalamus all day long through the hypophyseal portal system and reacts with anterior pituitary glands, causing it to release hormones called gonadotropin. The hormones are luteinizing hormone (LH) and stimulating follicle hormone (FSH) which have direct actions on testes for men and ovaries for women. LH and FSH are essential to stimulate the development of secondary sexual characteristics which can be seen during puberty and to maintain normal values of sex steroid such as testosterone in men and estrogen and progesterone in women [4, 5, 8, 9]. In Kallmann syndrome/HH, the release of GnRH is blocked or severely lacking. GnRH is released from hypothalamus by special neural cells or neurons. In the tenth weeks of brain development, GnRH neurons migrate from the source to hypothalamus [4, 5, 8].

GnRH neurons come from brain development area called olfactory placode; the neurons then pass cribriform plate and the structure is called *olfactory bulb*, where smelling sensations are originated from. From there the neurons migrate to the hypothalamus. If there is any problem with the development of the olfactory bulb, the progress of GnRH neurons can be blocked. If GnRH neurons cannot reach hypothalamus, there's no GnRH, causing declines of FSH and LH which caused failure of puberty and deficiency of testosterone in men and estrogen and progesterone in women. In Kallmann syndrome, there is no olfactory bulb, or it is not entirely developed, causing total olfactory sensation disorder (anosmia) or severely deficient olfactory sensation (hyposmia). Other forms of HH have normal development of olfactory bulb, so there's no olfactory sensation disorder, but GnRH neuron migration is influenced elsewhere and prevented the release of GnRH at the right time [2, 7, 11].

Most genes related to Kallmann syndrome/HH play roles in generation, migration or activities of GnRH neurons and have the abilities to stimulate the productions of LH and

FSH. Genetic relationship in Kallmann syndrome and other forms of HH is still unclear so far with around 70 % cases with an unknown cause. In this case, the patient has no genetic anomaly because chromosomal examination showed normal result [4, 12, 13]. Phenotype spectrum of Kallmann syndrome/HH includes classical hypogonadotropic-hypogonadism, adult-onset hypogonadotropic-hypogonadism, reversible Kallmann syndrome/HH, hypothalamic amenorrhea, and normal puberty without reproductive symptoms.

3.3. Therapy

The purposes of hypogonadism therapies in Kallmann syndrome are firstly to start virilization or breast development and secondly for fertility development. Therapies in Kallmann syndrome and other forms of hypogonadotropic-hypogonadism (HH) can be categorized into hormone replacement therapy and fertility therapy [1–3, 8].

The purpose of hormone replacement therapy (HRT) in men and women is to maintain normal hormone circulation (testosterone in men and estrogen/progesterone in women) equal to the normal physiological value in accordance to patients' ages. After optimal physical development is achieved with HRT administration, in men it is continued by maintaining normal androgynous functions such as libido, muscle development, energy level, hair growth, and sexual functions. In women, various types of HRT are administered for the menstrual cycle. HRT is very important for men and women to maintain bone density and reduce risks of early onset of osteoporosis.

Human chorionic gonadotropin (HCG) is sometimes used to stimulate testosterone production in men and induction of ovulation in women. Human menopausal gonadotropin (hMG) is used to stimulate sperm production in men and double egg production and induction of ovulation in women.

Fertility therapy includes administering gonadotropin LH and FSH to stimulate the production and release of eggs and sperms. Women with Kallmann syndrome or HH have advantages over men if the normal ovaries contain normal number of eggs and sometimes it takes a few weeks of therapy to reach fertility, while in men therapy can last up to 2 yr to reach fertility.

In this case, the patient was given one cycle of hormone replacement therapy with Angelique (estradiol 1 mg and drospirenone 2 mg) and Estero pills on 1 d to 21 d, the combination with Prothyra pills on 11 d to 21 d. The result of these treatments was the patient was finally able to have her first menstruation after the administration of the drugs. The effects of the drugs were to build her endometrial wall but only for a temporary moment.

Once the pills are stopped, the patient will not undergo her menstruation phase anymore because of the hormone production of her pituitary gland is inadequate. This medication also gave more strength to her bones due to her osteoporosis condition.

4. Conclusions

Kallmann syndrome is a developmental disorder combined with hypogonadotropic-hypogonadism and anosmia or hyposmia which is lack of or reduced olfactory. This hypogonadism is caused by gonadotropin-releasing hormone (GnRH) deficiency and is the result of the failure of synthetic embryonic migration of gonadotropin-releasing hormone neurons to the forebrain. Kallmann syndrome diagnosis, in this case, is based on anamnesis of amenorrhea and anosmia, a physical examination which did not discover secondary sexual characteristic growth including undeveloped breasts, lack of armpit hair, and lack of pubic hair. Supporting examination showed a decline of gonadotropin hormone, USG showed uterine hypoplasia, BMD showed osteoporosis, and chromosomal examination showed the normal result. Patient's therapy, in this case, included hormone replacement therapy and fertility therapy. Hormone replacement therapy is used to prevent her from severe osteoporosis while the fertility therapy is given to influence her periods. Due to her small uterus and mini vagina, we still have to face other problems such as difficulty in sexual activities and the possibility of pregnancy.

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