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Case Report

A rare disease of Kallmann syndrome: A case report ☆

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ABSTRACT

Kallmann syndrome (KS) is a rare genetic disorder that refers to the association between hypogonadotropic hypogonadism and anosmia or hyposmia due to abnormal migration of olfactory axons and gonadotropin-releasing hormone-producing neurons. Here, we present a case of a 40-year-old man who presented with psychological problems (emotional disturbance) as the chief complaint. Physical examination revealed gynecomastia, absence of facial and axillary hair, and sparse pubic hair, micropenis, undescended right testicle, low libido and lack of sexual function. A related finding is anosmia, a high-pitched voice. Hormonal analysis revealed hypogonadotropic hypogonadism profile, and chromosomal examination revealed a normal male karyotype. Abdominal ultrasound showed normal organs, and scrotal ultrasound showed an undescended right testicle (UDT) and small testes. Brain MRI revealed pituitary gland hypoplasia and olfactory bulb agenesis. These findings are characteristic of KS. He underwent orchidopexy dextra. He is now on a regular follow-up. Hormone replacement therapy is planned. Thus, besides medical treatments, psychological care is an integral component of the treatment strategy for this patient.

Introduction

Kallmann syndrome (KS) is a rare genetic disorder that refers to an association between hypogonadotropic hypogonadism and olfactory dysfunction (anosmia or hyposmia) due to abnormal migration of olfactory axons and gonadotropin-releasing hormone-producing neurons. It was first described by Maestre de San Juan in 1856 and characterized as a hereditary condition by Franz Josef Kallmann in 1944. In 1969, Bardin et al. found that individuals with KS had low gonadotropin levels. In the last decade, findings from research on the embryogenesis of olfactory sensory neurons and genetic mutations were incorporated to the description and diagnostic criteria assigned to KS [1–4].

KS has an incidence of 1 in 8000 to 30,000 in males and 1 in 40,000 to 120,000 in females. The estimated incidence of KS in males is 4-5 times higher than in females, and only 30% of cases have an identifiable genetic cause [5–7].

Hypogonadotropic hypogonadism and hyposmia or anosmia are the 2 main symptoms of KS. Cryptorchidism and gy-

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necomastia are common and micropenis occurs in approximately 50% of affected males. The primary hormonal defect is a failure of gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus, leading to secondary testicular failure [1,5,6].

The psychological problems of KS patients are non-ignorable, especially among male adolescents, and include depression, anxiety, and decreased quality of life that leads to low self-esteem and other effects. Because of the self-contempt, KS patients may hesitate to communicate with others. Thus, besides medical treatments for physical symptoms, psychological care is an indispensable component of the treatment strategy for KS patients [6].

History taking, physical examination, hormonal analysis, chromosomal examination, and imaging modalities are needed to establish KS. Clinical diagnosis of KS in adults is depending on the co-existence of anosmia with signs of hypogonadotrophic hypogonadism. However, the diagnosis may be difficult to establish in patients of pre-pubertal age and may require genetic testing and MRI. MRI is the modality of choice in assessing the absence of olfactory bulbs [2,7].

Case presentation

A 40-year-old man came to Dr. Hasan Sadikin General Hospital Bandung with psychological problems as the chief complaint, emotional disturbance, feeling inferior, include depression, anxiety, and decreased quality of life that leads to low self-esteem, because of the lack of secondary sexual characteristics. He has a small penis (micropenis), the penis is only slightly protruding, lack of sexual function, erectile dysfunction, and inability to ejaculate, low libido, and it is recognized that there is a decrease in sexual activity. He was circumcised. He was previously married, but they have divorced. Besides psychological care, counseling, and medication, further examinations/investigations are still needed.

The patient was born full term via normal spontaneous delivery to a 28-year-old mother. He is the second child of 5 siblings. Micropenis was observed but no further consultation was sought. He had never smelled anything, a family history of anosmia in the family is not found. He admitted that his voice was high-pitched. History of seizures, blurring of vision, color blindness, heart problems, and hearing loss was denied. Previous trauma history was denied. The patient had normal developmental milestones and no intellectual impairment.

Physical examination showed an adult male profile with a weight of 81 kg, height 175 cm, and a body mass index of 26kg/m^2. However, it shows the presence of gynecomastia, absence of facial and axillary hair, sparse pubic hair, micropenis and undescended right testicle, with a penile length of 1.5 cm. His secondary sexual characteristics were in Tanner stage 2 (Fig. 1). Neurologic examinations were normal, except for an olfactory disturbance.

A hormonal analysis described the hypogonadotropic hypogonadism profile. It revealed total testosterone levels of 9.7 ng/dL (normal value 249-836 ng/dL), luteinizing hormone (LH) levels of < 0.07 IU/mL (normal range 0.57-12.07), follicle stimulating hormone (FSH) levels of 0.34 IU/mL (normal value 0.95-11.95). The Estrogen was within the normal limits with a serum level of 87.5 pg/mL (normal value 60-190 pg/mL).

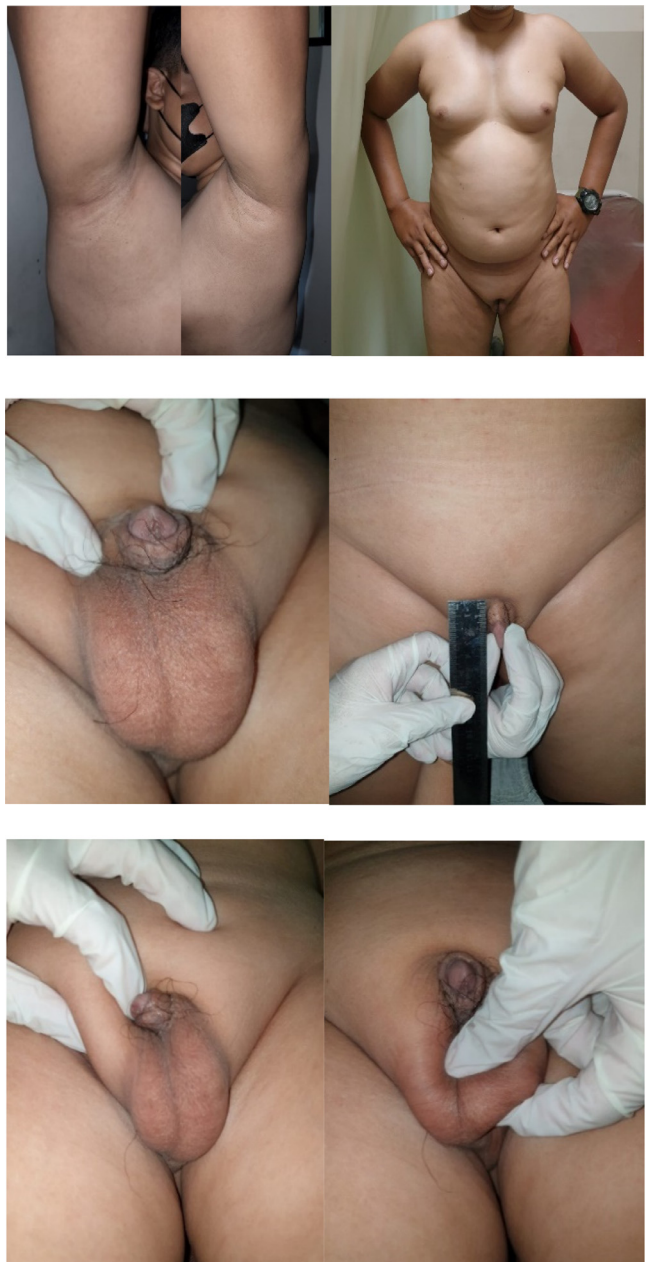

Fig. 1 – Physical examination gynecomastia, absence of facial hair and axillary, sparse pubic hair, micropenis and undescended right testicle.

Genetic profile or chromosomal examination in this patient showed a 46XY pattern, karyotyping was normal male (Fig. 2). Underdeveloped external genitalia, undescended testicle, and micropenis were the most likely syndromes. These findings are consistent with features of hypogonadism.

Abdominal ultrasonography showed normal organs. The findings of scrotal ultrasonography were small testes with un-

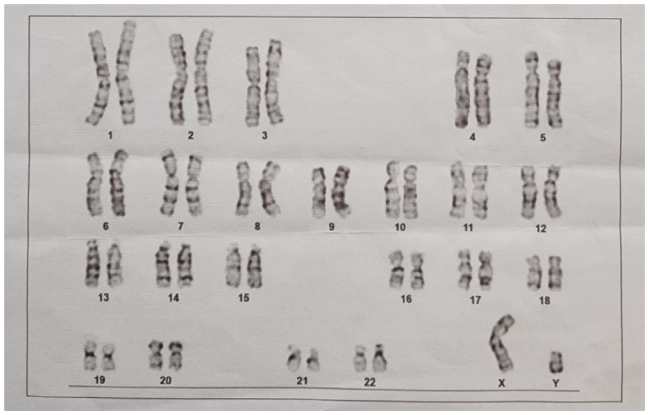

Fig. 2 – Chromosomal examination revealed a 46XY karyotype pattern.

descended the right testicle (UDT) and the position of the left testicle in the scrotum. The volume of the right and left testes was 0.1 cc and 0.52 cc, respectively (Fig. 3).

Brain MRI findings of this patient revealed a pituitary gland hypoplasia, which was 1.32×0.78×0.37 mm with a volume of 198 mm^3 (N: 380 mm^3), and an absent of the olfactory bulb (Fig. 4).

Based on a detailed history taking, physical examination, hormonal analysis, chromosomal examination, abdominal and scrotal ultrasonography, and brain MRI, this patient is consistent with KS.

The patient then underwent orchidopexy dextra (Fig. 5). Hormone replacement therapy (HRT) is planned. Follow-up will be regularly conducted. The psychological problems in this patient cannot be ignored. Thus, in addition to medical treatment of the physical symptoms, psychological care is an indispensable component of the treatment strategy for this patient.

Discussion

KS is a rare genetic disorder that refers to an association between hypogonadotropic hypogonadism and olfactory dysfunction (anosmia or hyposmia) due to abnormal migration of olfactory axons and gonadotropin-releasing hormone-producing neurons, which are the 2 main symptoms of KS. In male adolescents, absent and/or minimal virilization, low libido, and lack of sexual function are the common symptoms. Cryptorchidism, gynecomastia, and micropenis occur in approximately 50% of affected males, as in our patient. Absence of breast development and/or primary amenorrhea are the most common complaints in female adolescent [1–9].

KS was first described by Maestre de San Juan in 1856 and characterized as a genetic disorder by Franz Josef Kallmann in 1944. In 1969, Bardin et al. found that individuals with KS had low gonadotropin levels. In the last decade, findings from research on the embryogenesis of olfactory sensory neurons and genetic mutations were incorporated to the description and diagnostic criteria assigned to KS [1–4].

KS is a genetically heterogeneous disease, has an incidence of 1 in 8000 to 30.000 in males and 1 in 40.000 to 120.000 in females. The estimated incidence of KS in males is 4-5 times higher than in females, and only 30% of cases have an identifiable genetic cause [5–7].

GnRH or luteinizing hormone-releasing hormone (LHRH), a decapeptida, is essential for mammalian puberty onset and reproduction. The reproductive function is mainly managed by 1200-1500 GnRH neurons, and these unique neurons have either an olfactory placode/ectodermal or neural crest cell origin. GnRH is produced by the arcuate nucleus in the hypothalamus and delivered to the anterior pituitary through pituitary portal blood vessels, where it pulsatively stimulates the synthesis and secretion of LH and FSH that participate in gonadal maturation and function in both man and women [6].

In 1989, Schwanzel-Fukuda et al. and Wray et al. proved that GnRH neurons were unusual neuroendocrine cells derived from progenitor cells outside the central nervous system in the medial olfactory placode that migrated across the nasal septum, entered the forebrain with the nervus terminalis, and finally arched into the septal-preoptic area and hypothalamus. Several years later, similar spatiotemporal migration and developmental patterns of GnRH neurons were confirmed in early human embryos. KS, a neuronal migration defect in humans, is caused by disruption of olfactory axon development and GnRH neuron migration. LHRH-expressing cells were found to be absent in the KS fetuses, although dense clusters of LHRH cells and fibers were present in the nose. The developmental relationship between the GnRH system and the olfactory system illustrates some of the pathogenesis and clinical features in KS patients [6].

The hypothalamic-pituitary-gonadal (HPG) axis is activated from mid-trimester, restrained at the end of gestation, and reactivated after birth. In early childhood (6 months of the age in boys; 3-4 years of age in girls), GnRH pulsatile secretion is actively inhibited and persists until adolescence. Reactivation of GnRH release after this quiescent period marks the initiation of puberty, but the mechanisms involved in triggering of puberty remain unclear. During puberty, GnRH regulates the synthesis and release of FSH and LH. In boys, FSH promotes proliferation of immature Sertoli cells and spermatogonia, while LH stimulates Leydig cells to produce testosterone, leading to initiation of spermatogenesis. In girls, FSH and LH are essential for follicular maturation and ovulation [6].

Clinical diagnosis of KS in adults is depending on the coexistence of anosmia with signs of hypogonadotrophic hypogonadism. However, the diagnosis may be difficult to establish in patients of prepubertal age and may require genetic/chromosomal analysis and MRI. Moreover, even though anosmia is present from birth, it is not apparent to either the parents or the child. The diagnosis is only made when puberty does not occur. Occasionally, the diagnosis is made earlier due to investigation of other associated anomalies, including cardiovascular abnormalities, renal agenesis, cryptorchidism, midline defects, sensorineural deafness, small anterior lobe of the pituitary gland, short fourth metacarpal and facial anomalies (cleft lip and palate) [2].

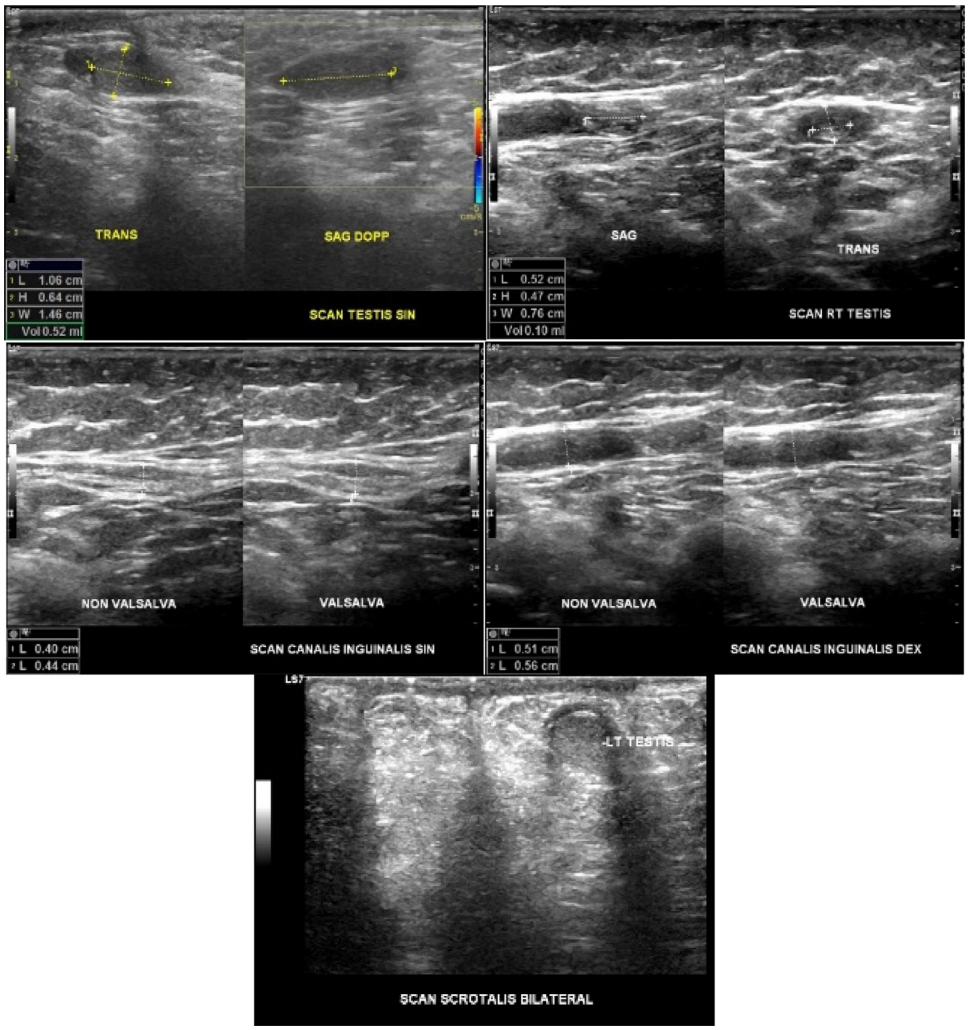

Fig. 3 – Scrotal ultrasonography undescended the right testicle (UDT) and the volume of the right and left testes was 0.1 cc and 0.52 cc, respectively.

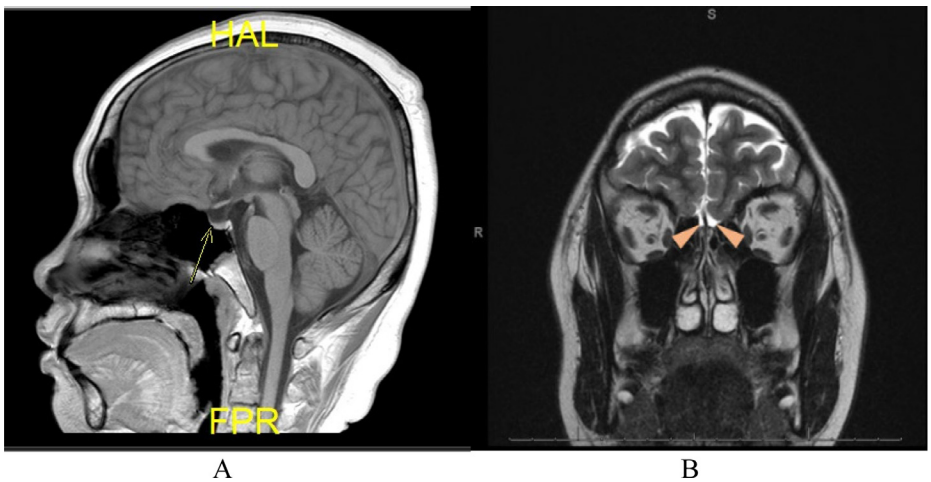

Fig. 4 – Brain MRI. (A) Pituitary gland hypoplasia (arrow), (B) an absent of the olfactory bulb (arrow).

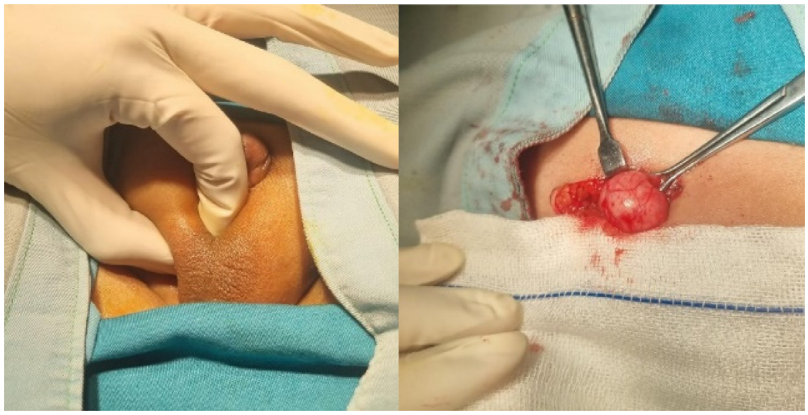

Fig. 5 – The patient underwent orchidopexy dextra.

Genetics molecular of KS

In KS more than 30 genes are mutated. Mutated and loss-of-function genes, one of which is the ANOS1 gene (also known as KAL1), the first and most common pathogenic gene for KS first identified in 1991, is inherited through the X-linked recessive pattern. The mutated genes in patients with KS include: ANOS1, FGFR1, FGF8, FGF17, IL17RD, DUSP6, SPRY4, FLRT3, KLB, SEMA3A, SEMA3E, SEMA7A, PLXNA1, PROK2, PROKR2, SOX10, FEZF1, HESX1, TUBB, HS6ST1, CHD7, WDR11, AXL, and CCDC141. It is thought that mutations of these gene, and other similar genes, results in failure of appropriate migration of gonadotropin-releasing hormone-secreting cells and olfactory neurons during embryogenesis [6,9,10].

MRI in KS

MRI is the modality of choice in assessing the absence of olfactory bulbs. In fact, the introduction of MRI into clinical practice in the early 80s has greatly improved the value of radiological approach to olfactory disorders by allowing precise depiction of the olfactory bulb and olfactory tract, and very sensitive detection of even very little damage to the central projection areas of the sense of smell. In the mid-90s, the pioneering works by Yousem et al. demonstrated the ability of MRI to yield accurate volumetric measurements of the olfactory bulb in various pathological conditions. This had major clinical relevance because the olfactory bulb is a unique central nervous organ, in which size and function closely correlate [2,11].

A coronal scanning with large matrix size and decreased intersection gap is recommended to visualize the olfactory bulbs optimally. It is the best suited plane for anatomical olfactory tract overview, detection of parenchymal lesions and olfactory bulb volumetry. Axial MR images allow the visualization of the olfactory sulci of the frontal lobes; however, they did not evaluate the patients' olfactory bulbs or tracts, which are optimally visualized in coronal planes. The sagittal sequences in thin slices objectify the tract within the olfactory sulcus, but their lower sensitivity makes them more useful to the study of the pituitary gland, the corpus callosum or the posterior fossa. Gadolinium injection is not usually necessary. In some cases, it helps differentiate the bulbs of the nasal mucosa, which is enhanced. High resolution coronal fast spin echo T2- and T1-weighted images are the preferred sequences for a morphologic evaluation of the olfactory system. Olfactory bulbs are normally seen as well-defined structures along cribriform plate. Olfactory sulci are seen between gyrus rectus and medial orbital gyrus [2].

MRI findings in KS include absent or hypoplastic olfactory sulci and olfactory bulbs. A hypoplastic anterior pituitary may also be seen. Koenigkam-Santos et al. found that olfactory bulb and sulcus aplasia were the most common findings in KS patients, and demonstrated agreement between MRI findings, especially the presence of bulb aplasia and anosmia [2,11].

Held et al. studied olfactory fibers, bulb, tract, and sulcus by MRI in 30 healthy volunteers, using 2D turbo spin echo sequences, 3D MP-RAGE (Magnetization Prepared Rapid Gradient Echo), and 3D CISS (Constructive Interference Steady State). They found that both 3D sequences were superior to 2D turbo spin echo, and MP-RAGE was better than CISS. Therefore, they recommend including MP-RAGE sequence in the MRI protocol of the olfactory nerve [2,11,12].

Management for KS

Early diagnosis and treatment of KS are crucial, because they can lead to improved quality of life and prevention of disease-related complications, especially during adolescence as the vital period for secondary sexual maturation and critical point for adolescent psychological development [6].

Surgical surgery is the first choice for newborns with cryptorchidism at 6-12 months. HRT promotes virilization, development of muscle mass and strength, pubertal growth spurt, deepening of voice, growth of penis, libido, and sexual function in males and furthers development of breast in females. HRT could also improve skeletal maturation and bone mass density, self-confidence, and well-being in both genders. It should be noted that HRT prescriptions are different depending on the main goal and age of KS [6,7].

Low-dose testosterone is used to induce penis growth of male newborns after surgery. For adolescent male lacking puberty, sex steroid therapy (testosterone in KS male patients) or

gonadotropin, including human chorionic gonadotropin (hCG) and FSH are used for pubertal induction and the development of normal secondary sexual characteristics. To recover the fertility in KS adult males, pulsatile GnRH and gonadotropins are used for treatment [6,7].

In adolescent girls, 17β-estradiol is administrated to induce puberty, and progesterone is added during the last 14 days of the menstrual cycle after breakthrough bleed or full breast development. Estrogen-progesterone therapy is also recommended for the KS females without fertility intention. For the women with fertility desire, pulsatile GnRH/gonadotropin treatment is suggested to mimic physiological condition. After timely and appropriate HRT, KS patients can develop secondary sexual characteristics, maintain normal sex hormone levels, lead a healthy sexual life, and achieve fertility. KS patient generally requires lifelong treatment, surprisingly, however, 10%-20% patients show spontaneous reversal of reproductive function, although subsequent relapse can occur [6,7]. Although current treatment markedly improved quality of life in KS patients, the genetic characteristics of KS mean that there is some risk of transmitting the mutated genes to offspring and presenting severe symptoms [6].

The psychological problems of KS patients are non-ignorable, and include depression, anxiety, and decreased quality of life that leads to low self-esteem and other effects. Because of the self-contempt, KS patients may hesitate to communicate with others. Thus, besides medical treatments for physical symptoms, psychological care is an indispensable component of the treatment strategy for KS patients [6].

Conclusion

In conclusion, KS is a rare genetic disorder that refers to the association between hypogonadotropic hypogonadism and anosmia or hyposmia due to abnormal migration of olfactory axons and gonadotropin-releasing hormone-producing neurons, which are the 2 main symptoms of KS. Cryptorchidism, gynecomastia and micropenis occur in about 50% of affected men. The primary hormonal defect is the failure of gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus which causes secondary testicular failure [1,2,5,6].

History taking, physical examination, hormonal analysis, chromosomal examination, and imaging modalities are an important role in finding the hallmarks of KS. The psychological problems of KS patients are non-ignorable, and include depression, anxiety, and decreased quality of life that leads to low self-esteem and other effects. Because of the self-contempt, KS patients may hesitate to communicate with others. Thus, besides medical treatments for physical symptoms, psychological care is an indispensable component of the treatment strategy for KS patients [2,6,7].

Purpose of the study

The purpose of this study is to add insight based on a real case of a patient with Kallmann syndrome.

Confidentiality

All personal data obtained are confidential which are guaranteed by the author. The author will not publish personal information of subjects that is not related to research interests.

Participation

Subject participation in this study is voluntary. Subject will not be compensated for the participation in this study. Subject may withdraw his/her participation at any time. Subject may also choose not to participate in this study.

Risks

Subject will not be compensated for his/her participation. However, subject will have the satisfaction of contributing to our knowledge and understanding of Kallmann syndrome.

Informed consent

Subjects voluntarily participate in this study. Subjects agree that Subjects have given the opportunity to ask questions and have them answered to subject satisfaction.

Patient consent

Written informed consent for the publication of this case report was obtained from the patient.

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