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Kallmann Syndrome- causes, symptoms, treatment- review of literature

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Abstract

Background: Kallmann syndrome is a rare congenital disorder characterized by hypogonadotropic hypogonadism and anosmia or hyposmia. KS results from abnormalities in the migration of GnRH neurons from the nasal placode to the hypothalamus. The prevalence of KS is estimated to be approximately 1:30,000 in males and 1:125,000 in females. KS manifests at various stages of life, ranging from the neonatal period through adolescence to adulthood. In the neonatal period, boys may present with cryptorchidism and micropenis, while symptoms in girls may be less apparent. During adolescence, patients often experience the absence or incomplete development of secondary sexual characteristics. In adulthood, KS often leads to

infertility, cardiovascular issues, and neurological symptoms. Diagnostic methods include olfactory tests and hormonal analysis, assessing levels of gonadotropins, testosterone, LH and FSH. MRI can reveal structural abnormalities in the olfactory system.

Aim of study: The goal of this article was to gather information about the Kallmann syndrome, focusing on its epidemiology, etiology, characteristic features, and treatment strategies.

Materials and Methods: A review of the literature available in the "PubMed", Google Scholar and Medline databases. The search was performed by using following keywords: "kallmann syndrome", "anosmia", hypogonadotropic hypogonadism".

Results and conclusions: Kallmann syndrome is a complex condition that necessitates a multifaceted approach to diagnosis and treatment. Early identification of the disorder is crucial, allowing for the timely initiation of appropriate hormonal therapy and psychological support, which significantly improves the quality of life for patients. Further research into the genetic and neurobiological mechanisms of KS is essential for the development of more effective therapeutic and diagnostic methods.

Keywords: Kallmann syndrome; anosmia; hypogonadotropic hypogonadism

Introduction

Kallmann syndrome (KS) is a rare congenital disorder characterized by hypogonadotropic hypogonadism and anosmia or hyposmia (1). It was first described by the French physician François Kallmann in 1944, who conducted a study on the co-occurrence of hypogonadism and anosmia in three families affected by this condition (2). He demonstrated that both anosmia and hypogonadism were co-inherited in all affected individuals, confirming the hereditary nature of this syndrome. In the 1950s, Swiss anatomist de Morsier (3)provided a detailed description of the disease, examining the underdevelopment or absence of the olfactory bulbs and tracts in several men with hypogonadism. Gonadal dysfunction arises from

abnormalities in the differentiation or migration of neurons that embryologically originate in the nasal placode and migrate to the hypothalamus, where they function as gonadotropin-releasing hormone neurons. A deficiency in gonadotropin-releasing hormone (GnRH) leads to reduced levels of sex hormones, resulting in a lack of sexual maturation and secondary sexual characteristics (4). Most cases are diagnosed during adolescence due to delayed sexual development; however, Kallmann syndrome can also be suspected in male infants with cryptorchidism, micropenis, or other concomitant reproductive disorders (5). Characteristic clinical symptoms include a lack of spontaneous puberty onset and partial or complete anosmia in both sexes (6). Genes implicated in Kallmann syndrome include KAL1 (Xp22.32), which is inherited in an X-linked recessive manner; FGFR1 (8p12), FGF8 (10q25-q26), CHD7 (8q12.2), and SOX10 (22q13.1), which follow an autosomal dominant inheritance pattern; and PROKR2 (20p12.3) and PROK2 (3p21.1), which can be inherited in both autosomal recessive and oligogenic forms (7) . Further research is needed to confirm whether other genes, such as SEMA3A, which are suspected to be involved in Kallmann syndrome, are indeed causative. The exact prevalence of Kallmann syndrome remains undetermined, but it is estimated to be approximately 1:30,000 in males and 1:125,000 in females (8).

Clinical course

Characteristic features of Kallmann syndrome include congenital hypogonadotropic hypogonadism (CHH) and anosmia or hyposmia. The functioning of the hypothalamic-pituitary-gonadal (HPG) axis changes throughout life, allowing for appropriate diagnosis of KS at various stages (7). The symptoms of KS can be categorized into three phases, considering the impact of GnRH on human development: the neonatal and childhood period, adolescence, and adulthood (Figure 1) (9).

Neonatal and Childhood Period

In male neonates, typical manifestations of GnRH deficiency include cryptorchidism and micropenis (a penile length of less than 2.5 cm) (5). These characteristics result from low levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a deficit

of testosterone in males and estrogen and progesterone in females (10). In female neonates with GnRH deficiency at this stage, there are no specific clinical symptoms (4).

Adolescence

Low levels of GnRH in patients with KS lead to incomplete or absent sexual maturation. In boys, this manifests as insufficient or absent virilization, low libido, and a lack of sexual function. In girls, the most common complaints are underdeveloped breasts and/or primary amenorrhea (11).

Adulthood

Diagnosis of Kallmann syndrome in adulthood is often associated with infertility and, occasionally, with early onset of osteoporotic fractures (12). Some men with KS may exhibit gynecomastia or lack of facial hair, which can lead to psychological issues and affect normal life. In adult women with KS, in addition to congenital hypogonadotropic hypogonadism and hyposmia/anosmia, cardiovascular disorders (such as fatigue, dyspnea, cyanosis, palpitations, and syncope) and neurological symptoms (including hearing loss, epilepsy, and paraplegia) may occur, though they tend to be less severe than in men.

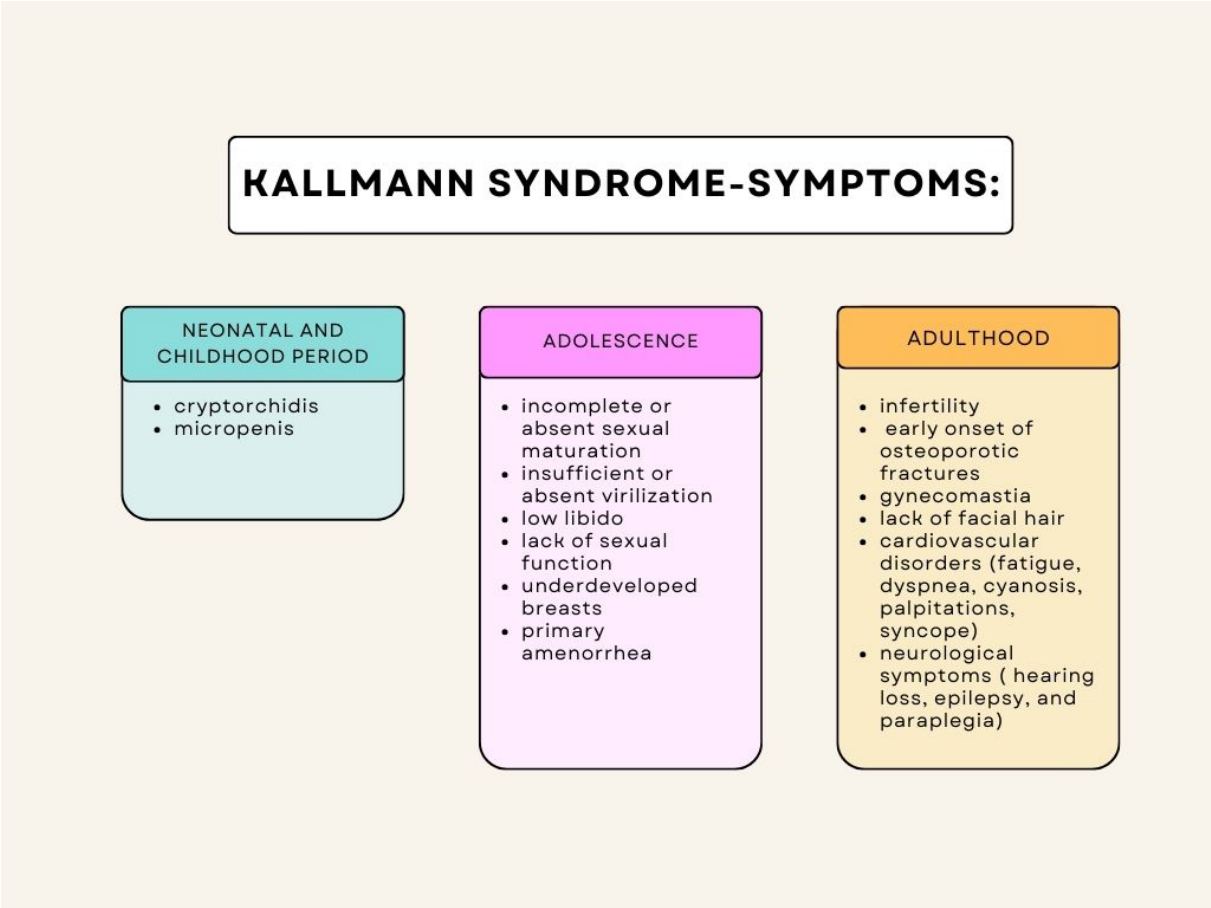

Figure 1. Most common symptoms in Kallmann syndrome in men and women in the respective age groups (9).

In addition to the primary manifestations of Kallmann syndrome, congenital abnormalities are often present, including cleft palate and lip, hypodontia, and malformations of the upper or lower limbs, as well as finger bone anomalies (such as polydactyly, syndactyly, and camptodactyly) (13). Unilateral renal agenesis is also observed (14). Neurological disorders may occur, including central hearing impairment, synkinesis, and ataxia. Patients with KS often exhibit poor balance due to cerebellar ataxia, skeletal anomalies (such as scoliosis, polydactyly, and clinodactyly), and pigmentary defects (15). Color blindness and orbital abnormalities have also been observed in patients with Kallmann syndrome (16). Psychological issues represent a significant aspect of KS, particularly among adolescent boys, and include depression, anxiety, and reduced quality of life, leading to low self-esteem and other negative outcomes (17). Studies of patients with congenital hypogonadotropic hypogonadism have shown elevated scores on assessments such as the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), and the Arizona Sexual Experiences Scale (ASEX), indicating substantial psychological

difficulties (18). Due to low self-esteem, patients with Kallmann syndrome may avoid social interactions, particularly during adolescence when their emotions are unstable (19). Therefore, in addition to medical treatment for physical symptoms, psychological support is an essential component of the treatment strategy for patients with KS.

Diagnosis

The clinical diagnosis of Kallmann syndrome involves the evaluation of congenital hypogonadotropic hypogonadism and hyposmia or anosmia (1). Diagnosing KS may be based on reproductive system-related symptoms, such as a history of cryptorchidism and/or micropenis, delayed sexual maturation and/or absence of secondary sexual characteristics, reduced libido, and infertility (15). Due to the subjective nature of self-reported olfactory function, formal olfactory tests are necessary to assess hyposmia or anosmia. During the first few months after birth, a temporary activation of the hypothalamic-pituitary-gonadal axis, referred to as "mini-puberty" (20). During this period, testosterone levels rise in both boys and girls, and in girls, estradiol levels also increase. Minipuberty, observed in infants aged 1-3 months, serves as an indicator for diagnosing congenital hypogonadotropic hypogonadism. Outside of minipuberty, CHH is most diagnosed during adolescence or early adulthood. Therefore, hormonal analysis provides valuable indicators for diagnosing Kallmann syndrome. Patients of both sexes with KS exhibit very low plasma levels of gonadotropins, including FSH, LH and inhibin B. Notably, during mini-puberty, serum testosterone levels (in boys) and FSH and LH levels (in both boys and girls) show a transient increase, which is exceptionally low in infants with congenital hypogonadotropic hypogonadism (21). Additionally, some changes in brain structure have been observed in patients with KS. Magnetic resonance imaging (MRI) studies can reveal abnormalities in the olfactory fossae, such as unilateral or bilateral agenesis of the olfactory bulb or olfactory tracts, reduced depth, decreased curvature, or increased thickness of the olfactory cortex within the olfactory sulcus in patients with Kallmann syndrome (22–24). However, in a small number of patients with confirmed anosmia, the olfactory structures may appear normal. In these cases, anosmia or hyposmia may be attributed to other factors, such as viral infections, trauma, or drug-induced olfactory disorders. In cases where mutations in the FGFR1, FGF8, KAL1, or CHD7 genes are present in the family, fetal ultrasonography can assist in detecting skeletal abnormalities, cleft lip/palate, renal agenesis, and other developmental anomalies.

Although these diagnostic criteria are important, a crucial aspect of diagnosing Kallmann syndrome is the exclusion of other potential diagnoses. The main differential diagnoses for KS include tumors causing acquired hypogonadotropic hypogonadism, constitutional delay of growth and puberty (CDGP), CHARGE syndrome, and functional hypogonadotropic hypogonadism (25). Among these diagnoses, constitutional delay of growth and puberty (CDGP) is the most challenging to distinguish from Kallmann syndrome because both conditions are associated with delayed puberty (26). Delayed puberty is defined as the delay in the onset or progression of puberty by more than 2–2.5 standard deviations below the population mean, including the absence of testicular enlargement (<4 mL) by age 14 in boys and lack of breast development by age 13 in girls (27). Differences in testicular size, the presence of cryptorchidism and/or micropenis, CHH-related phenotypes, and genetic testing can provide partial diagnostic clues to help differentiate KS from CDGP (28).

Treatment

Early diagnosis and treatment of Kallmann syndrome are crucial, as they can significantly improve quality of life and prevent complications associated with the condition, particularly during adolescence. This period is critical for the development of secondary sexual characteristics and plays a key role in the psychological development of adolescents (7). As previously mentioned, the primary symptoms of Kallmann syndrome are congenital hypogonadotropic hypogonadism and hyposmia/anosmia, with CHH being the most burdensome symptom for patients with KS. It is important to note that the preferred treatment method for infants with cryptorchidism aged 6–12 months is surgical intervention. Hormone replacement therapy aids in virilization, muscle mass and strength development, accelerated growth during puberty, voice deepening, penile growth, libido, and sexual function in males, as well as breast development in females (29). Hormone replacement therapy (HRT) can also enhance skeletal maturation, bone mineral density, self-esteem, and overall well-being in both sexes. The guidelines for HRT vary depending on the primary objective and the age of the patients with KS. Low doses of testosterone are used to induce penile growth in male infants following surgery. In adolescent males who have not reached puberty, sex steroid therapy (testosterone) or gonadotropins (including human chorionic gonadotropin [hCG] and follicle-stimulating hormone [FSH]) are administered to induce puberty and the development of normal secondary sexual characteristics (30). To restore fertility in adult males with Kallmann

syndrome, pulsatile GnRH and gonadotropins are used. In adolescent females, 17β-estradiol is administered to induce puberty, with progesterone added during the last 14 days of the menstrual cycle after breakthrough bleeding or full breast development (5). Estrogen-progestin therapy is also recommended for women with KS who do not plan to expand their family. For women with reproductive plans, pulsatile GnRH/gonadotropin therapy is advised to mimic physiological conditions (31). With timely and appropriate hormone replacement therapy, patients with KS can develop secondary sexual characteristics, maintain normal levels of sex hormones, lead a healthy sexual life, and achieve fertility. Patients with KS typically require lifelong treatment; however, approximately 10–20% of patients experience spontaneous restoration of reproductive function, although disease relapse may occur (32).

Prognosis

Kallmann syndrome is not life-threatening. With hormonal treatment, appropriate feminization or virilization is achieved for all patients during puberty. Although current treatment methods significantly improve the quality of life for patients with KS, the genetic nature of the condition implies a certain risk of transmitting mutated genes to offspring and the potential for severe symptoms. In most cases, fertility can be achieved, although the presence of cryptorchidism significantly affects the prognosis in males.

Summary

Kallmann syndrome is a rare yet significant disorder that affects various aspects of patients' physical health and psychosocial well-being. Early diagnosis and appropriate treatment are crucial for improving the quality of life for these individuals (33). Advances in genetic and neurobiological research contribute to a better understanding of the mechanisms underlying this syndrome and the development of more effective therapeutic methods. Collaboration among various specialists, including endocrinologists, neurologists, geneticists, and psychologists, is essential for the comprehensive management of Kallmann syndrome.

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