Kallmann Syndrome — Diagnosis and Treatment

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Kallmann's syndrome is one form of reproductive failure due to severe hypogonadism that is associated with complete loss of the sense of smell. Kallmann's syndrome is a genetic disorder and several genes such as KAL1, FGFR1, FGF8, and PROKR2 have been associated with the condition. While KAL1 is responsible for the x-linked inherited form of the disease, the other genes are found in patients with autosomal dominant Kallmann’s syndrome. Hormonal replacement therapy is indicated to correct severe hypogonadism.

Definition of Kallmann Syndrome

Kallmann's syndrome is a genetic condition in which there is a complete or incomplete loss of the sense of smell and severe hypogonadism that is associated with infertility and delayed/absent puberty.

Epidemiology of Kallmann Syndrome

Most cases of Kallmann’s syndrome are inherited by an x-linked pattern, hence more common in men. It is estimated that 1 in 8,000 males is going to be affected by Kallmann’s syndrome while 1 in 40,000 females might have the condition. Additionally, the presentation in men is usually more severe and girls are likely to have only mild hypogonadism.
Etiology and Pathophysiology of Kallmann Syndrome

Most cases of Kallmann’s syndrome are sporadic; yet, studying familial cases help to identify candidate genes for the disorder, understand the pathophysiological changes responsible for the phenotype and determine genetic testing in sporadic cases.

Over 20 genetic abnormalities have been associated with Kallmann’s syndrome. However, the most commonly identified genes in Kallmann’s syndrome are the KAL1, FGFR1, PROKR2, PROK2, CHD7, ANOS1, and FGF8. KAL1 mutations are responsible for the x-linked form of the disease, FGFR1 and FGF8 are associated with an autosomal dominant form, while PROKR2 and PROK2 present with incomplete loss of smell and atypical Kallmann’s syndrome.

KAL1 gene encodes the extracellular matrix glycoprotein anosmin-1. FGFR1 encodes fibroblast growth factor receptor 1 while FGF8 encodes for fibroblast growth factor 8. PROKR2 and PROK2 encode prokineticin receptor 2 and prokineticin-2 respectively.

Not only the clinical phenotype of mutations in these genes is different, but the type of the mutation in each gene is thought to be different from the others. Nonsense, frameshift, and deletions mutations have been identified in the KAL1 gene for instance, while patients with the PROKR2 and PROK2 mutations usually have a loss of function mutations. FGFR1, an FGF8 mutation are usually missense.

The exact mechanism of how these genes eventually lead to the loss of the sense of smell and hypogonadism is still poorly understood. The most celebrated theory is that these genes are the source of abnormal migration of the olfactory nerves cells from the nose area to form the olfactory bulb in the brain. They also influence the neurons that take part in the formation of GnRH within the hypothalamus.

Additionally, the variability in phenotype presentation in families with the same mutations points towards an important role of either epigenetics or interplay between other disease-modifying genes which are yet to be discovered.

Clinical Presentation of Kallmann Syndrome

Kallmann’s syndrome, like any other form of reproductive disorders, usually presents with signs and symptoms of hypogonadism.

Boys usually present during puberty due to small testes, micropenis, undescended testis and lack of secondary sexual characteristics such as deepening of the voice and male pattern of hair growth. Men who present later in life usually complain of infertility associated with the loss of the sense of smell. It is important to understand that the loss of the sense of smell is variable in Kallmann’s syndrome and can be incomplete; therefore, formal testing of anosmia is usually indicated.

Females might present with decreased fertility and primary amenorrhea, but hypogonadism in girls is usually milder, hence the diagnosis can be delayed.

A family history of anosmia or hypogonadism might be evident in a few cases. It is essential to identify the mode of inheritance as it can guide genetic testing and imaging studies later. Additionally, the presence of associated features, such as cleft
palate, point towards a possible FGFR1 or FGF8 mutation, while an incomplete loss of the sense of smell might indicate a PROKR2 or PROK2 mutation.

**Diagnostic Workup for Kallmann Syndrome**

Patients with Kallmann’s syndrome usually present with a **pubertal delay** with or without a previous history of cryptorchidism.

**Laboratory investigations** are indicated to confirm hypogonadism. Patients have hypogonadotropic hypogonadism, meaning testosterone, follicle-stimulating hormone, and luteinizing hormone are all decreased or deficient. If the patient also has anosmia or hyposmia, then the diagnosis of Kallmann’s syndrome is confirmed. For patients who do not have anosmia if they have a family history of anosmia, the diagnosis of Kallmann’s syndrome is “suspected.”

Patients with anosmia should undergo magnetic resonance imaging of the olfactory bulb before starting genetic testing. The olfactory bulbs are very small on MRI in patients with Kallmann’s syndrome. MRI also helps in excluding other conditions such as a pituitary or hypothalamic lesion responsible for the hypogonadism.

Patients with hypogonadism, normal sense of smell, but a family history of anosmia, should undergo genetic testing for PROKR2, PROK2, FGF8, and FGFR1 mutations. Patients with anosmia and hypogonadotropic hypogonadism, but no family history of anosmia, should also undergo the same genetic testing.

Men who have a family history of Kallmann’s typical syndrome and an x-linked pattern of inheritance should undergo KAL1 testing. Patients with a family history of cleft lip and palate in addition to Kallmann’s syndrome might have an FGFR1 or FGF8 mutation. A family history of Kallmann’s syndrome that is associated with sleeping or eating disorders indicates possible PROKR2 or PROK2 mutations.

Once the diagnosis of Kallmann’s syndrome is confirmed and the mutation responsible is identified, it becomes easy to identify whether the mutation was inherited or a de novo mutation. **De novo mutations** in FGFR1 and FGF8 are responsible for at least one-third of the cases. Additionally, genetic testing about the risk of Kallmann’s syndrome in future offspring becomes possible once the responsible mutation and the mode of inheritance are determined.

**Treatment of Kallmann Syndrome**

The treatment of Kallmann’s syndrome mainly focuses on correcting hypogonadism which is usually successful in starting the development of secondary sexual characteristics and correcting infertility in most of the cases.

Treatment of Kallmann’s syndrome should be staged and the expectations should be set clear before starting hormonal replacement therapy. The first step should focus on initiating virilization or breast development, depending on the gender of the patient.

Men have usually prescribed testosterone which stimulates the development of secondary sexual characteristics. Females should be prescribed combined estrogen and progesterone hormone replacement therapy develop secondary sexual characteristics such as normal pubic hair and breast development.
Men or women who seek fertility might benefit from gonadotropins administration. Gonadotropins administration can achieve fertility in most cases. Gonadotropin-releasing hormone pulsatile administration can also be used to achieve fertility.

Currently, postnatal administration of testosterone is being evaluated in infants with a confirmed diagnosis of Kallmann’s syndrome. Such infants are usually in families with a known history of Kallmann’s syndrome because genetic testing is not routinely done unless there is a documented increased risk of the condition.

Postnatal hormonal replacement therapy is hypothesized to result in a postnatal sudden increase in gonadotropins which might influence reproductive and sexual prognosis later.

References


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