Kallmann syndrome and ichthyosis: a case of contiguous gene deletion syndrome

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Summary

Kallmann syndrome is a genetically heterogeneous form of hypogonadotropic hypogonadism caused by gonadotropin-releasing hormone deficiency and characterized by anosmia or hyposmia due to hypoplasia of the olfactory bulbs; osteoporosis and metabolic syndrome can develop due to longstanding untreated hypogonadism. Kallmann syndrome affects 1 in 10 000 men and 1 in 50 000 women. Defects in 17 genes, including \( \text{KAL1} \), have been implicated. Kallmann syndrome can be associated with X-linked ichthyosis, a skin disorder characterized by early onset dark, dry, irregular scales affecting the limb and trunk, caused by a defect of the steroid sulfatase gene (\( \text{STS} \)). Both \( \text{KAL1} \) and \( \text{STS} \) are located in the Xp22.3 region; therefore, deletions in this region cause a contiguous gene syndrome. We report the case of a 32-year-old man with ichthyosis referred for evaluation of excessive height (2.07 m) and weight (BMI: 29.6 kg/m\(^2\)), microgenitalia and absence of secondary sex characteristics. We diagnosed Kallmann syndrome with ichthyosis due to a deletion in Xp22.3, a rare phenomenon.

Learning points:

- Kallmann syndrome is a genetically heterogeneous disease characterized by hypogonadotropic hypogonadism with anosmia or hyposmia associated with defects in the production or action of gonadotropin-releasing hormone (GnRH) and hypoplasia of the olfactory bulbs.
- Several genes have been implicated in Kallmann syndrome, including \( \text{KAL1} \), located in the Xp22.3 region, which is responsible for X-linked Kallmann syndrome. \( \text{KAL1} \) encodes the protein anosmin-1. X-linked ichthyosis is caused by deficiency of the steroid sulfatase enzyme, encoded by \( \text{STS} \), which is also located in the Xp22.3 region. Deletions involving this region can affect both genes and result in contiguous gene syndromes.
- Phenotype can guide clinicians toward suspicion of a specific genetic mutation. \( \text{KAL1} \) mutations are mostly related to microgenitalia, unilateral renal agenesis and synkinesia, although patients need not present all these abnormalities.
- Longstanding untreated hypogonadism is associated with poor sexual health, osteoporosis and metabolic syndrome with the concomitant risk of developing type 2 diabetes mellitus and obesity.
- Treatment aims to promote the development of secondary sex characteristics, build and sustain normal bone and muscle mass and restore fertility. Treatment can also help minimize some psychological consequences.
- Treatments available for patients with congenital GnRH deficiency such as Kallmann syndrome include gonadal steroid hormones, human gonadotropins and GnRH. The choice of therapy depends on the goal or goals.
Background

Kallmann syndrome is a genetically heterogeneous disease characterized by hypogonadotropic hypogonadism with anosmia or hyposmia associated with defects in the production or action of gonadotropin-releasing hormone (GnRH) and hypoplasia of the olfactory bulbs. Kallmann syndrome affects 1 in 10 000 men and 1 in 50 000 women. Inheritance can occur through autosomal dominant, autosomal recessive and X-linked recessive modes. The inheritance mode is important for genetic counseling, because there is a risk not only of pubertal disorders in carriers’ children, but also of other, potentially life-altering anomalies unrelated to reproduction (1, 2, 3, 4, 5).

Several genes have been implicated in Kallmann syndrome, including KAL1, PROK2, PROKR2, FGF1, FGF8, NEFL, CHD7, WDR11, SEMA3A, HS6ST1, HESX1, SOX10, FGF17, IL17RD, DUSP6, SPRY4 and FLRT3 (3, 4). X-linked Kallmann syndrome involves defects in KAL1 (also called ANOS1 before the HGNC gene nomenclature). KAL1 gene is located in the Xp22.3 region; this gene contains 14 exons encoding anosmin-1, a neural cell adhesion molecule protein involved in fibroblast growth factor signaling (3).

Correct anosmin-1 expression is crucial for the migration of GnRH neurons to the ventral hypothalamus during embryogenesis (6). KAL1 is the most penetrant of the genes causing congenital GnRH deficiency in patients with KAL1 mutations and their families. X-linked KAL1 mutations have never been reported in families with normosmic idiopathic hypogonadotropic hypogonadism or in families with both anosmic and nonanosmic individuals.

X-linked ichthyosis, characterized by early onset dark, dry and irregular scales affecting the limb and trunk, is caused by deficiency of the steroid sulfatase enzyme (2). Steroid sulfatase is encoded by the STS gene, which like KAL1, is located in the Xp22.3 region. X-linked ichthyosis affects about 1 in 6000 males (7).

The manifestations of KAL1 alterations are particularly severe. These mutations are associated with low blood levels of gonadotropin and sex steroid levels throughout life and with a high incidence of microphallus, cryptorchidism and small testes, which can be observed during the neonatal period. Midline facial defects such as cleft lip/palate may also be present. Manifestations that become evident during childhood include anosmia or hyposmia, unilateral renal agenesis, synkinesia, ataxia, visual symptoms, hearing loss, dental agenesis, scoliosis, kyphosis, excessive joint mobility, short fourth metacarpal bones, clinodactyly, foreshortened limb bones and flat feet. Thus, it is crucial to carry out a thorough examination to search for other abnormalities that can guide us to the abnormal genetic region. The strong associations with microgenitalia, unilateral renal agenesis and synkinesia can help clinicians suspect KAL1 mutations (8, 9).

At first, many cases appear to be sporadic, but family history often belies this assessment and indentifies familial cases, so a thorough history of the proband and other family members is essential. Critical clues are anosmia, absence of menstrual periods, family history of delayed puberty and the presence of other malformations (skeletal, renal, cardiac) in close family members. Hypogonadotropic hypogonadism can lead to osteoporosis, metabolic syndrome and infertility (3).

Patients with Kallmann syndrome, like those with other congenital GnRH deficiencies, can be treated with gonadal steroid hormones, human gonadotropins and GnRH. The choice of treatment depends on the goal or goals, which may include fostering the development of secondary sex characteristics, building and sustaining normal bone and muscle mass, and/or restoring fertility (10). The KAL1 gene is also thought to be expressed in the germ cells at specific stages of differentiation in the adult testes, suggesting that it may participate directly in gametogenesis in the testes (4). Testosterone therapy is indicated when the aim is to promote the development of secondary sex characteristics (e.g., in pubertal boys), testicular descent and penis growth. Not only will testosterone therapy not induce gonadal maturation, but it also suppresses intratesticular testosterone production and is thus directly harmful to fertility prospects.

Case presentation

A 32-year-old man with congenital ichthyosis managed in our hospital's Dermatology Department was referred to our endocrinology department for the evaluation of excessive height and weight and small genitalia. He had a previous history of anosmia and poor development of secondary sex characteristics (scant facial hair and body hair development, no increase in muscle bulk, failure of the voice to deepen and adipomastia).

He was born after traumatic labor with forceps delivery (at birth, weight: 3850g, length 59 cm) and had some learning difficulties during childhood. His mother reported he was also emotionally immature. He completed elementary school. The Wechsler Adult Intelligence
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test (WAISS-III) revealed an intelligence quotient of 92 (normal).

He underwent circumcision for phimosis at the age of 14 years.

Physical examination found height 207 cm, weight 127 kg, BMI 29.6 kg/m² (overweight), arm length 201 cm and abdominal distribution of adipose tissue. Tanner stage was G2P2 with an impalpable right testis and a left testis measuring 2 cm in diameter (4 mL). He had dark, dry, irregular scales on his limbs and trunk (Fig. 1 and 2).

He had a healthy, 178-cm-tall younger brother. His father’s height was 170 cm and mother’s height was 163 cm. His family medical records showed no history of delayed development, synkinesia or renal, dental, mental or neurologic abnormalities.

Investigation

Scrotal ultrasound showed that the undescended right testis measured 17 mm in diameter and had coarse calcifications inside; the left testis measured 14 mm in diameter. Both testes were hypoechoic without tumors inside. Abdominal ultrasound showed both kidneys were normal, and blood tests showed normal renal function. Baseline hormone concentrations in plasma were testosterone: 0.12 ng/mL (2.49–8.36), FSH: 0.25 IU/mL (1.5–12.4), LH: <0.1 IU/mL (1.7–8.6) and prolactin: 7.67 ng/mL (4.04–15.2). In 1994, pituitary magnetic resonance imaging (MRI) showed pituitary hypoplasia (height, 3.6 mm). In 2013, another MRI showed the absence of olfactory bulbs and tracts in both sides. Bone densitometry revealed osteoporosis of the spine (Z-score −4.45 s.d., 0.816 g/cm²).
Karyotype was 46,XY. He was diagnosed with hypogonadotropic hypogonadism associated to ichthyosis.

Genotype/phenotype correlations in patients with different-sized deletions or translocations involving Xp22.3 have enabled the establishment of the map position of several genes associated with different X-linked disorders. These disorders can occur from the effects of deletion on a single gene alone or in combination with the effects of the deletion of neighboring genes, which results in a contiguous gene syndrome \(^{(11)}\). Therefore, to look for a genetic relation between these two diseases, we extracted genomic DNA samples from peripheral leukocytes. A microarray-based comparative genomic hybridization test found a pathogenic copy-number variant: arr(hg19)Xp22.32p22.31 (4 699 972–9 427 600) >0, which contains 12 genes: NLGN4X, VCX3A, HDHD1, STS, VCX, PNPLA4, MIR651, VCX2, VCX3B, KAL1, FAM9A and FAM9B. Of these, VCX3A is linked with intellectual disability.

Tests on blood samples from his parents revealed that the deletion was inherited from his mother, although she had no symptoms of either disease. Males with deletions in distal Xp are nullisomic for the respective regions, so their disease phenotype depends on the extent of the deletion. As KAL1 partially escapes X-inactivation, the Kallmann syndrome phenotype is comparatively rare among females who carry heterozygous KAL1 mutations \(^{(11)}\).

**Treatment**

As our patient desired only to achieve secondary sex characteristic development, he was empirically treated with 100 mg intramuscular testosterone propionate supplementation every 28 days in progressive doses. A few months later, the treatment was changed to 1000 mg testosterone undecanoate every three months, which maintained testosterone levels within the normal range.

**Outcome and follow-up**

He showed progressive muscular development, deepening of the voice, development of facial hair and penis enlargement, achieving Tanner stage P3G3 with a left testis measuring 3 cm in diameter (5–6 mL), and his bone densitometry values improved (spine Z-score −3.68 s.d., 0.911 g/cm²).

Despite grade I obesity (BMI 34.6 kg/m²), his glucose metabolism was normal. He has been referred to our dietitian for a hypocaloric diet to lose weight and to facilitate changes to a healthier lifestyle.

**Discussion**

Kallmann syndrome, a genetically heterogeneous disease, can be associated with other diseases in a contiguous gene syndrome. Therefore, it is very important to investigate related conditions and diseases (in our case, ichthyosis, a skin disease) to provide additional information to arrange for the most accurate tests to establish a diagnosis.

KAL1 mutations are particularly severe, being associated with a high incidence of microphallus, cryptorchidism and small testes, which can be observed during the neonatal period, and with low levels of gonadotropins and sex steroids in blood samples. Gynecomastia does not typically occur in GnRH deficiency syndromes such as Kallmann syndrome.

It is also essential to carry out a thorough examination to investigate other abnormalities that can orient us to the genetic abnormality. KAL1 mutations are mostly related to microgenitalia, unilateral renal agenesis and synkinesia \(^{(8)}\). Therefore, phenotype can help raise suspicion of this mutation.

Routine karyotype analysis is not sensitive enough to detect subtle chromosome rearrangements (<5 Mb). New genomic tests are becoming more readily available to help clinicians make the diagnosis, but sufficient knowledge of the different techniques is required to choose the most accurate test. Microarray-based comparative genomic hybridization can detect submicroscopic chromosomal deletions and duplications and as well as subtle DNA copy-number changes.

However, since patients <18 years old are often referred for delayed onset of puberty, clinicians must differentiate between hypogonadotropic hypogonadism and constitutional growth delay as causes, which might be suggested by a family history of slow or ‘stalled’ puberty. In Kallmann syndrome, the secretion of adrenal androgens is unaltered and can produce adrenarche, some pubic hair can be present. By contrast, in constitutional delay of puberty patients’ poor growth velocity results in delayed skeletal maturation and short stature, and adrenarche is attenuated \(^{(3)}\). Indicators of delayed (but existing) puberty are early evidence of breast or testicular development. Before genetic testing, it is important to rule out a family history of GnRH deficiency, anosmia and/or the presence of one or more associated congenital abnormalities that suggest congenital GnRH deficiency.
It is very important to diagnosis Kallmann syndrome as early as possible because men diagnosed after adolescence suffer from infertility and osteoporosis or even pathological bone fractures (3).

Treatment aims to promote the development of secondary sex characteristics, build and sustain normal bone and muscle mass, restore fertility and prevent long-term metabolic complications of hypogonadism such as developing type 2 diabetes mellitus (3). Treatment consists of testosterone replacement through daily application of testosterone gels and intramuscular injections of long-acting testosterone preparations such as testosterone undecanoate. Young patients (around 12 years old) usually begin treatment with low dose testosterone (e.g., 50 mg testosterone enanthate monthly, 10 mg transdermal testosterone every other day, or 40 mg oral testosterone undecanoate daily) and the dose is gradually increased to full adult dosing over 18–24 months. Such regimens aim to mimic natural puberty and help maximize statural growth while allowing time for psychosexual development and minimizing the risk of precocious sexual activity. Patients in late adolescence or early adulthood (as in our case) with lack of pubertal development often undergo more aggressive treatment involving higher initial testosterone doses (e.g., 200 mg testosterone enanthate monthly or every 2–3 weeks; the frequency of injections should be guided through levels of testosterone) (3).

Inducing full spermatogenesis would require the administration of human chorionic gonadotropin (hCG) and menopausal gonadotropins or recombinant FSH. Administering hCG, which has the biologic activity of LH, stimulates the Leydig cells of the testes to synthesize and secrete testosterone. If the sperm count fails to reach 5–10 million/mL and/or pregnancy has not occurred 6 months after serum testosterone reaches 400–800 ng/dL (13.87–27.7 nmol/L), human menopausal gonadotropin (hMG); a preparation used for its FSH, but which also contains LH) can be added. FSH increases cell proliferation (hMG; a preparation used for its FSH, but which also contains LH) can be added. FSH increases cell proliferation and thus possibly improves spermatogonial stem cell function (12).

In summary, Kallmann syndrome can be challenging to diagnose, but timely diagnosis and treatment to induce puberty can be beneficial for sexual, bone and metabolic health, and might help minimize some of the psychological consequences. Patients typically require lifelong treatment and special attention to complications such as osteoporosis, infertility and type 2 diabetes mellitus (3).


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