CASE REPORT

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Challenges in The Management of Kallmann Syndrome: A Case Report

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ABSTRACT

Kallman syndrome is combined disorder of hypogonadotropic hypogonadism and anosmia. Incidence of congenital hypogonadotropic hypogonadism is 1-10:100,000 live births, and approximately 2/3 and 1/3 of cases are caused by Kallmann syndrome and idiopathic hypogonadotropic hypogonadism, respectively. We report a man, 35 years old, with complaints of small penis, small voice, impaired smell, gynecomastia, narrowing of visual field, mustache not growing, little pubic and armpit hair. Patients underwent surgery on both breasts with histopathological results of gynecomastia, no malignancy. Testicular ultrasound results showed bilateral testicular atrophy. Laboratory results showed karyotype 46XY, Follicle-stimulating hormone 1.79 mIU/mL, Luteinizing hormone 1.49 mIU/mL, testosterone <0.03 ng/mL, estradiol 5.0 pg/mL, prolactin 6.75 ng/mL and prostate-specific antigen 0.473 ng/mL. Head CT scan imaging showed bilateral otitis media, mastoiditis and sinusitis. Patients were diagnosed with Kallmann syndrome, anxiety and depression symptoms (ADS) chronic tubotympanic suppurative otitis media, sinusitis, oculus dexter and sinister hemianopsia. Patient was treated with testosterone undecanoate injection 1000 mg IM every 3 months, levofloxacin 500 mg PO once daily, avamys nasal spray twice daily. Symptoms of Kallman syndrome can include absent or incomplete pubertal development, anosmia or hyposmia, and low sex steroid levels. KAL1 gene mutations cause Gonadotropin-releasing hormone (GnRH) deficiency, associated with Kallmann syndrome. Testosteron replacement is indicated for men who already have children or have no desire for children. Surgery should be considered as the last option in patients with considerable discomfort, psychological stress, cosmetic problems, long-standing gynecomastia (>12 months) and suspected malignancy. The aim of testosterone therapy is to reverse the symptoms of hypogonadism, and surgery is last option in patients with considerable discomfort.

Keywords: Kallmann syndrome, small penis, gynecomastia, testosterone undecanoate**,** surgery

BACKGROUND

Kallmann syndrome (KS) is a clinically and genetically heterogeneous disorder, which combines hypogonadotropic hypogonadism with anosmia.[1,2] Congenital hypogonadotropic hypogonadism is a rare disorder that results from the failure of the normal episodic gonadotropin-releasing hormone (GnRH) secretion, leading to delayed puberty and infertility.[3] Congenital hypogonadotropic hypogonadism is often occurs in adolescence or afterward, and the disease is mostly due to developmental defects in GnRH neuron migration or in the maturation of the GnRH neuronal network and is often associated with congenital features congenital hypogonadotropic hypogonadism hypogonadism.[3]

Hypogonadism can result from a primary testicular disorder (hypergonadism) or occur secondary to hypothalamic-pituitary dysfunction (hypogonadotropic).[2] The incidence of congenital hypogonadotropic hypogonadism is approximately 1-10:100,000 live births, and approximately 2/3 and 1/3 of cases are caused by KS and idiopathic hypogonadotropic hypogonadism, respectively.[2]

CASE ILLUSTRATION

We report a man, 35 years old, with complaints of a small penis, small voice, impaired smell, enlargement of both breasts, mustache not growing, little pubic and armpit hair and narrowing of visual field. In February and April 2023, this patient underwent left and right breast surgery at Wates Regional Hospital with histopathological results of gynecomastia, and no malignancy was found. This patient was referred to Dr. Sardjito hospital and underwent several examinations. Bilateral testicular ultrasound results on June^{6th} 2023 were found bilateral testicular atrophy. Laboratory results showed karyotype 46 XY, decreased levels of testosterone

< 0.03 ng/mL, Luteinizing hormone (LH) 1.49 mIU/mL, and estradiol 5.0 pg/mL; Follicle-stimulating hormone (FSH) 1.79 mIU/mL, prolactin 6.75 ng/mL, and PSA 0.473 ng/mL. Head Computed Tomography scan (CT scan) imaging on September^{1st} 2023 impressions of bilateral otitis media, bilateral mastoiditis, sinusitis of frontal, ethmoidal, and bilateral maxillary. Evaluation of head Magnetic Resonance Imaging (MRI) results on June^{12th} 2024 impression, no visible pituitary adenoma; cavum septum pellucidum et vergae; no visible images of infarction, bleeding, infection or intracranial mass, and no nasal septum deviation visible.This patient was diagnosed with KS, anxiety and depression symptoms (ADS) Chronic tubotympanic suppurative otitis

Figure 1. Clinical features of patient with micropenis, and post-mastectomy

Table 1. Patient laboratory results

Laboratory results	26/5/23	6/6/23	30/10/23	18/11/23	27/12/23	17/4/24	10/6/24	Normal range
FSH	1.79							1.5-12,4 mIU/mL
LH	1.49							1.7-8,6 mIU/mL
Estradiol (E2)	< 5.00							11.3-43.2 pg/mL
Testosterone	< 0.03		0.10	1.55	3.27	2.42		2.8-8.0 ng/mL
Prolactin	6.75	2.00						4.6-21.4 ng/mL
Karyotype		46XY						
PSA totals					0.473			≤ 4.0 ng/mL
Urea							12	6-20 mg/dL
Creatinine							0.98	0.67-1.17 mg/dL

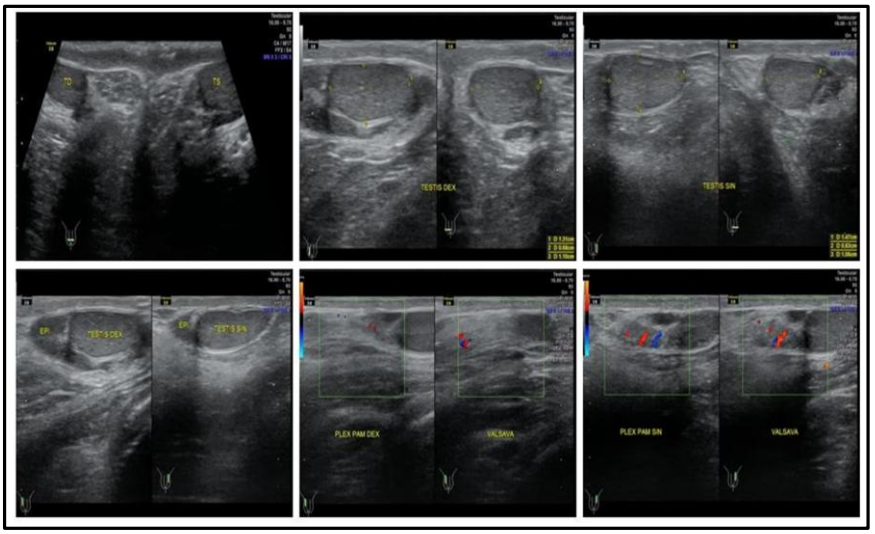

Figure 2. Ultrasound of the patient's testicles on June[6th] 2023, Impression of bilateral testicular atrophy (right testis measuring 1.31 x 0.68 x 1.x 1 cm; left testis measuring 1.47 x 0.83 x 1.05 cm). No varicoceles were seen in the bilateral testicles.

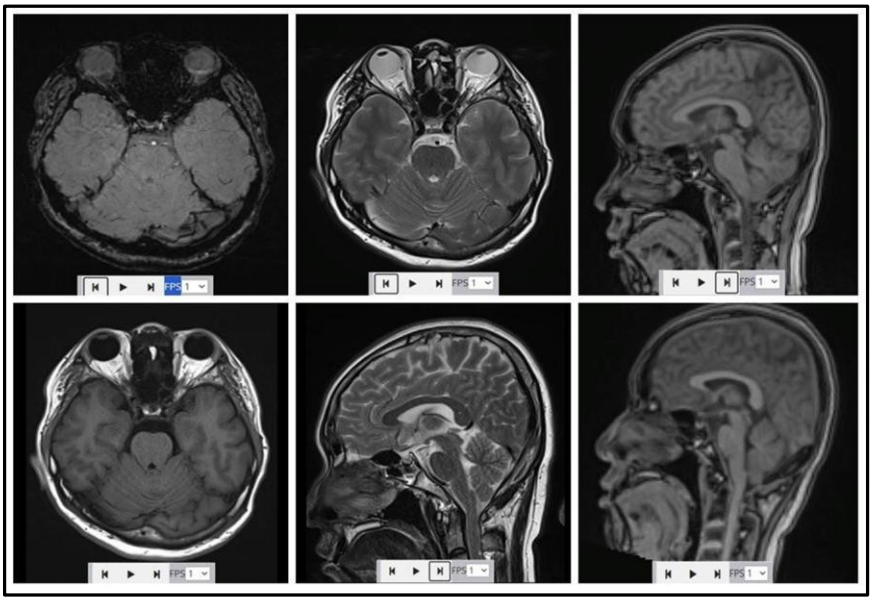

Figure 3. Head MRI results on June[12th] 2024, Impression, no visible pituitary adenoma; cavum septum pellucidum et vergae; no visible images of infarction, bleeding, infection or intracranial mass, and no nasal septum deviation visible.

media, sinusitis, Oculus Dextra et Sinister (ODS) hemianopsia. This patient was consulted by an ENT and Ophthalmologist. This patient was treated with testosteron (sustanon) injection 250 mg IM twice a week for 5 months and then continued with testosterone undecanoate (nebido) injection 1000 mg intramuscular (IM) every 3 months, levofloxacin 500 mg peroral (PO) once daily, folic acid 1 mg PO once daily, Avamys nasal spray twice daily. Patient follow-up revealed that the penis size slightly enlarged, voice slightly louder, and testosterone fluctuations increased.

DISCUSSION

Congenital hypogonadotropic hypogonadism is divided into anosmic hypogonadotropic hypogonadism KS and congenital normosmic isolated hypogonadotropic hypogonadism (idiopathic hypogonadotropic hypogonadism).[2] In hypogonadotropic hypogonadism, secretion of GnRH of pituitary is absent or inadequate.[2]

Analysis of KS gene mutations found mutations in KAL1, FGFR1, FGF8, PROK2, PROKR2, CHD7, and WDR11.[4] KAL1 gene mutations cause GnRH deficiency, associated with KS. KAL1 encodes the anosmin-1 protein, which plays a role in regulating GnRH neuron adhesion and axonal migration. This gene is mapped to the X- chromosome Xp22.32.[2] GnRH neurons are an unusual neuronal population, as they originate outside the central nervous system in the olfactory placode, and follow a complex migration route to reach their destination in the hypothalamus.[3]

To date, a molecular genetic diagnosis is attained in only approximately 30% of Kallmann syndrome patients, which implies the existence of additional genes underlying Kallmann syndrome.[4]

Diagnosis

For male infants, micropenis with or without cryptorchidism can be suggestive of congenital hypogonadotropic hypogonadism, and typically, low serum testosterone, LH, and FSH levels. However, hormonal testing is not routinely prescribed for male infants with micropenis or cryptorchidism.[3] Suspicion of KS in a patient if the following criteria are found:

1. Absent or incomplete pubertal development by the age of 18 years,
2. Anosmia or hyposmia based on either anamnestic information, formal testing (e.g. olfactometry), or testing with familiar odors,
3. Low circulating basal sex steroid levels in association with inappropriately low or normal gonadotropin levels, and subnormal or normal response to GnRH stimulation test.[4]

The symptoms of hypogonadotropic hypogonadism can include decreased libido, impaired erectile function, muscle weakness, increased adiposity, depressed mood, and decreased vitality.[2] Patients with Kallmann syndrome usually lack puberty, but the reproductive phenotype may vary from severe hypogonadism (cryptorchidism or micropenis in male infants) to reversal of hypogonadotropism later in life.[4] Gynecomastia is caused by an imbalance between estrogen and androgen action or an increased estrogen to androgen ratio, due to increased estrogen production, decreased androgen production or both.[5] Gynecomastia causes anxiety, psychosocial discomfort and a fear of breast cancer.[5]

The clinical characteristics of hypogonadotropic hypogonadism are androgen deficiency and delayed pubertal sexual maturation.[2] Complete physical examination can help the diagnosis which includes mirror movement assessment, measurement of testicular volume with a ruler (length × width^2 × 0.52), olfaction was assessed with smell testing (the 40-item smell testing from University of Pennsylvania Smell Identification Test, (UPSIT), where a score < 5 percentile on the UPSIT is classified as anosmic.[4]

A set of laboratory investigations can integrate evaluations such as testosterone, estradiol, sex hormone-binding globulin, LH, FSH, TSH, prolactin, human chorionic gonadotropin (hCG), alpha-fetal protein, liver and renal function tests.[6] Low blood testosterone levels and low pituitary hormone levels confirm the hypogonadotropic hypogonadism diagnosis.[2] In male, circulating testosterone levels in patients with congenital hypogonadotropic hypogonadism are usually low, that is, < 3 nmol/L (86.5 ng/dL).[3]

A prolonged stimulated intravenous GnRH test can be useful.[2] Inhibin B is a hormone secreted by sertoli cells and reflects sertoli cell number and function. Inhibin B is under the control of FSH. Healthy seminiferous tubules after puberty also regulate inhibin B production, likely through the control of spermatids. Most men with congenital hypogonadotropic hypogonadism with absent puberty with or without micropenis and cryptorchidism exhibit low serum inhibin B levels (< 30-60 pg/mL), indicating a reduced sertoli cell population. This is consistent with the absence of GnRH-induced FSH stimulation of the seminiferous tubules during fetal life and minipuberty. Higher serum inhibin B levels are encountered in a minority of patients with absent puberty but are found in most patients with partial puberty or acquired hypogonadotropic hypogonadism, consistent with a robust activation of the hypothalamus-pituitary-gonadal axis during minipuberty. Serum inhibin B levels correlated well with testicular size, and low inhibin B level is a negative predictor of fertility.[3]

During minipuberty, congenital hypogonadotropic hypogonadism infants have low anti mullerian hormon (AMH) levels, which can be normalized by Recombinant Follicle-Stimulating Hormone (rFSH) and Recombinant Luteinizing Hormone (rLH) treatment. rFSH treatment will induce proliferation of immature sertoli cells, and thus increases AMH levels; whereas hCG treatment will increase intratesticular testosterone levels and decreases AMH levels.[3]

Although an orchidometer is often used in clinical practice, testicular ultrasound has the advantage to assess not only testicular size but also testicular localization. The measurement of testicular size with ultrasound is important to determine the severity of GnRH deficiency and track the progress of testicular maturation during fertility treatment.[3] Besides that, ultrasound can assess the structure of the adrenals and kidneys. Cerebral magnetic resonance imaging (MRI) protocol was used to visualize the olfactory bulbs, sulci, and inner ears.[4] In Kallmann syndrome, cerebral MRI can show an anomalous morphology or even absence of the olfactory bulb.[2] Strategy for diagnosis of Kallmann syndrome is shown in figure 4.

Therapy

Early diagnosis and gonadotrophin therapy can prevent negative physical sequelae and mitigate psychological distress with the restoration of puberty and fertility in affected individuals.[7] Therapeutic goals in the adolescent male with congenital hypogonadotropic hypogonadism are to induce virilization, reach optimal adult height, acquire normal bone mass and body composition; achieve normal psychosocial development, and to gain fertility.[3]

There is no uniform KS treatment regimen used internationally.[3] The main medical intervention options include androgen, anti-estrogens, and aromatase inhibitors therapy. In male infants with severe GnRH deficiency, the main goals of hormonal treatment are to increase the penile size and to stimulate testicular growth. HCG therapy with or without a combination of nasal spray of GnRH has been shown to be effective to treat cryptorchidism in neonates and prepubertal boys. Combined gonadotropin therapy in male patients with

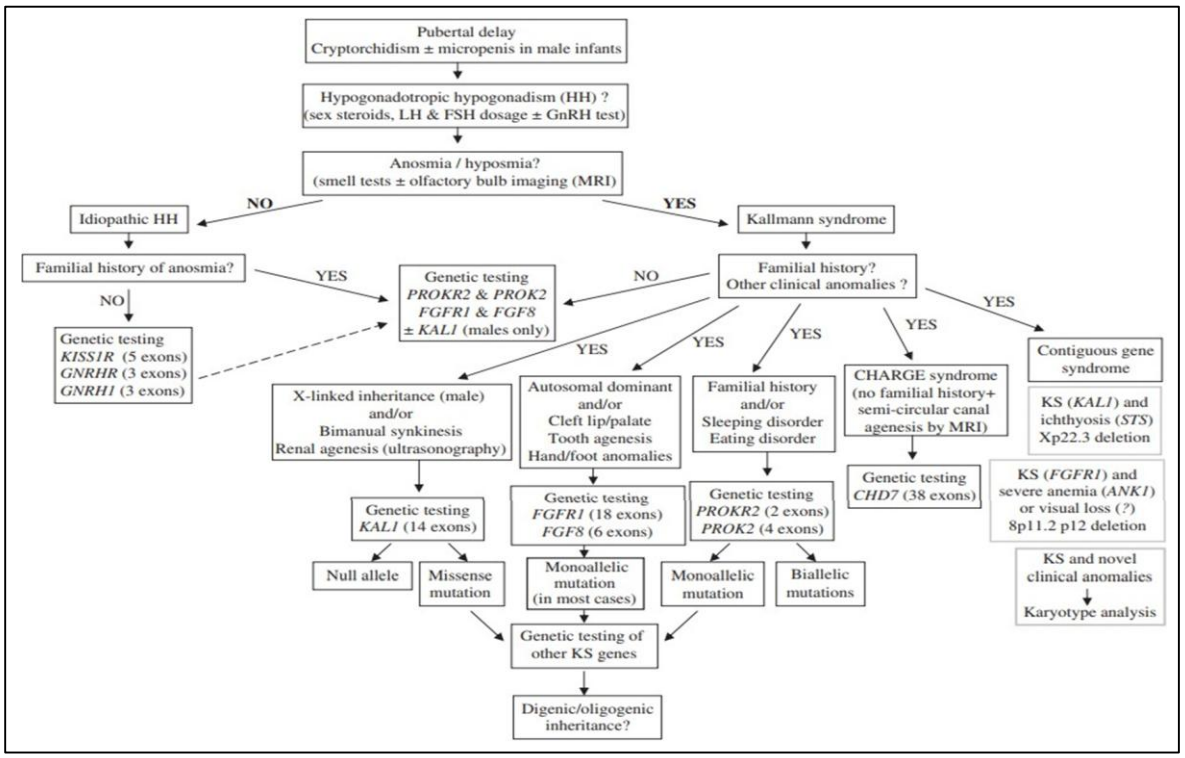

Figure 4. Genetic testing strategy for Kallmann syndrome.[1]

congenital hypogonadotropic hypogonadism during the neonatal period can have a beneficial effect on both testicular endocrine function and genital development, because it can stimulate sertoli cell proliferation and the growth of seminiferous tubules.[3]

Increasing testicular size correlates with the increase in sertoli cell mass, could lead to better outcomes in terms of sperm output during fertility induction in adolescence or adulthood. For patients with congenital hypogonadotropic hypogonadism seeking treatment in later adolescence or early adulthood, a higher dose of testosterone can be used to induce rapid virilization. Initial testosterone doses (such as 100 mg of testosteron enanthate monthly) can quickly increase to 250 mg IM monthly.[3]

Long-term androgen treatment is required in male patients with congenital hypogonadotropic hypogonadism to maintain normal serum testosterone levels, libido, sexual function, bone density, and general well-being. Of note, testosterone treatment does not stimulate testicular growth or spermatogenesis, because intragonadal testosterone production is needed to stimulate spermatogenesis. In contrast, increased testicular growth during testosterone treatment indicates congenital hypogonadotropic hypogonadism reversal and requires treatment withdrawal followed by monitoring of hormone profiling.[3] Fertility induction in male can be accomplished either by long-term pulsatile GnRH therapy or with combined gonadotropin therapy. This therapy will stimulate pituitary gonadotropin secretion and in turn intra gonadal testosterone production, resulting in the initiation and maintenance of spermatogenesis as evidenced by increased testicular volume and sperm output by 12 months of treatment on average.[3]

Induction of testicular maturation in adolescents can be given low doses of hCG (250 - 500 IU twice a week) with increasing increments of 250 – 500 IU every month, and rFSH was added once serum testosterone achieved targeted pubertal level (5,2 nmol/L). This treatment led to a substantial increase

in bitesticular volumes 5 ± 5 to 34 ± 3 mL and induction of spermatogenesis in 91 % of patients.[3] The hormonal treatment options for the induction of puberty in males with congenital hypogonadotropic hypogonadism are presented in table 2.

Table 2. Medical treatment of puberty induction, hypogonadism, and infertility in male patients with congenital hypogonadotropic hypogonadism.[3]

Treatment	Dosing and Administration	Advantages	Disadvantages
Induction of puberty in boys			
T enanthate	Initial dose: 50 mg IM monthly	Standard care with long clinical experience	Premature epiphyseal closure (high dose)
	↑ 50 mg increments every 6–12 mo	Aromatizable to E2: promote bone maturation	Could inhibit TV and spermatogenesis
	Up to 250 mg/mo		Impact on future fertility unknown
Gonadotropin	hCG: initial dose 250 IU SC twice weekly	Stimulate TV growth and spermatogenesis	Not standard treatment
	↑ 250–500 IU increments every 6 mo	Pre-FSH treatment can be beneficial in patients with TV ,4 mL or history of cryptorchidism	Need good compliance in adolescent patients
	Up to 1500 IU three times weekly		Need studies in larger cohorts
	rFSH: dose 75–150 IU SC three times weekly,		
Hypogonadism treatment in adult males			
T enanthate	250 mg IM every 2 to 4 wk	Cost-effective	Relatively frequent IM injection
	Interval adjusted based on trough T	Available around the world	SC route under investigation (302)
		Self-injection	
T undecanoate	1000 mg IM every 10 to 14 wk	Cost-effective	Interval of treatment highly variable follow-up of trough T is important
	Interval adjusted based on trough T	Infrequent injection	Injections by nurses
T gel	50–80 mg/d transdermally	Noninvasive	Risk of transmission by skin contact
		Self-administered	
Treatment of infertility in adult males			
Pulsatile GnRH	SC pump: 25 ng/kg per pulse every 120 min	Most physiological treatment	Not available in many countries
	Dose adapted based on serum T		Require centers with expertise
	Up to 600 ng/kg per pulse		Pituitary resistance (rare)
Gonadotropin	hCG: dose 500–1500 IU SC three times weekly,	Available around the world	Relatively expensive for rFSH
	Dose adjusted based on trough T	For patients with absent puberty (TV ,4 mL):	Frequent injections
	rFSH: dose 75–150 IU SC three times weekly,	Pre-rFSH treatment increases fertility prognosis	
	Dose adjusted based on serum FSH, sperm count		

hCG= Human chorionic gonadotropin ; rFSH= Recombinant Follicle-Stimulating Hormone ; IM= intramuscular ; SC= Subcutaneous

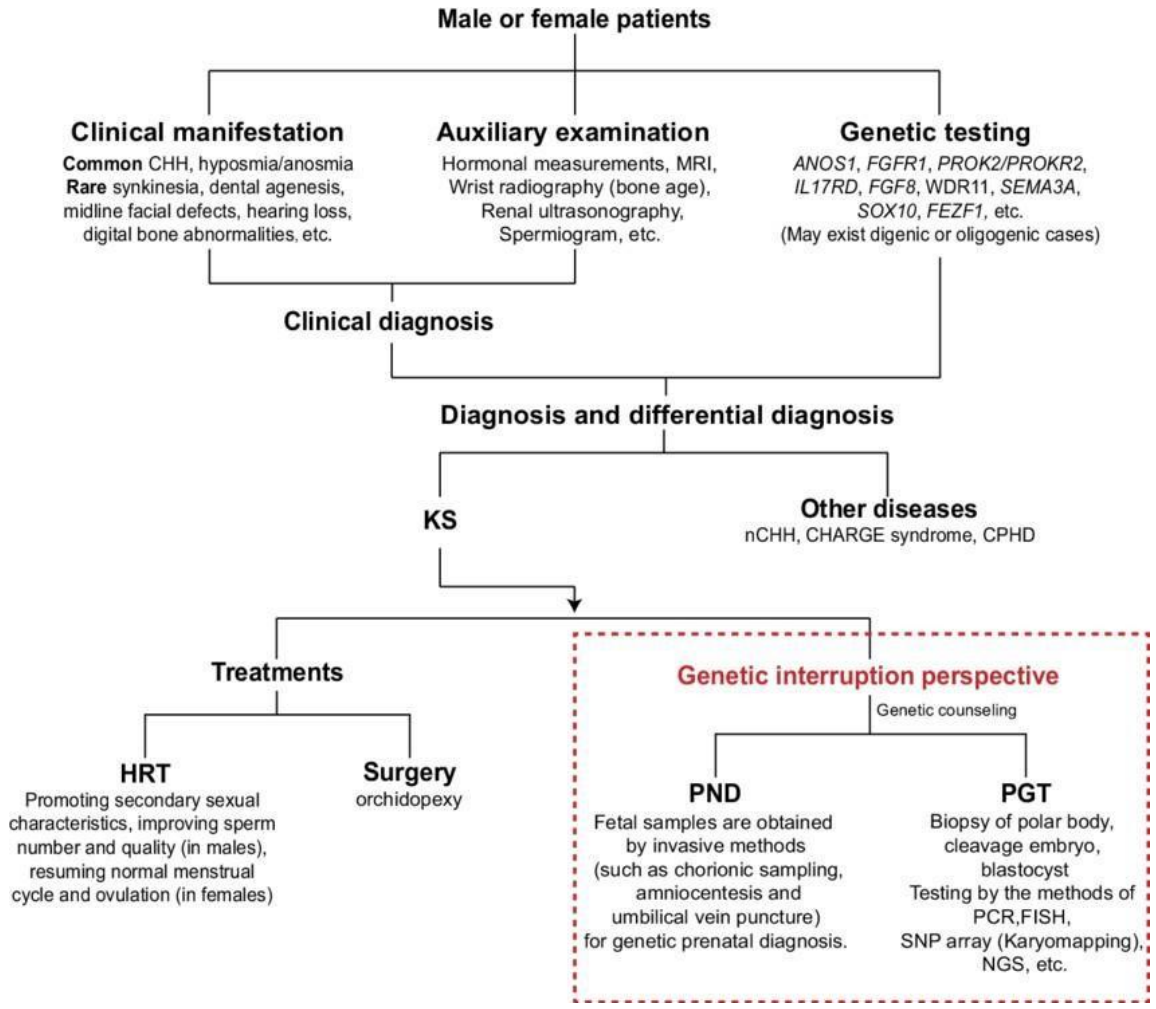

Figure 5. Diagram for clinical management and genetic interruption perspective of Kallmann syndrome.[8]

Cryptorchidism is a factor of poor prognosis for adult fertility and is also a risk factor for testicular malignancy.[3] Surgical orchidopexy is a surgical option for cryptorchidism.[3] Surgery is an option if gynecomastia persists for more than 1 year, complete regression is low due to the predominance of dense fibrous tissue, or gynecomastia is associated with severe pain, tenderness, and psychological distress. Surgery is not recommended in adolescents before the testicles reach adult size, because if surgery is performed before puberty is complete, breast tissue may be regrown.[5] The clinical management of Kallmann syndrome is shown in figure 5.

CONCLUSION

Kallmann syndrome is a clinically and genetically heterogeneous disorder, which combines hypogonadotropic hypogonadism with anosmia. The aim of testosterone therapy is to reverse the symptoms of hypogonadism, and GnRH or gonadotropin therapies are an option for men who want to have children. Surgery is the last option in patients with considerable discomfort.

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