Clinical Center of Vojvodina, Radiology Center, Novi Sad[1]
University of Novi Sad, Faculty of Medicine Novi Sad[2]
Clinical Center of Vojvodina, Clinic of Endocrinology, Diabetes and Metabolic Diseases, Novi Sad[3]
Institute for Child and Youth Health Care of Vojvodina, Novi Sad[4]
Health Center "Novi Sad", Novi Sad[5]

Case report
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TESTICULAR ULTRASOUND IN A PATIENT WITH KALLMANN SYNDROME – A CASE REPORT

ULTRAZVUK TESTISA KOD KALMANOVOG SINDROMA – PRIKAZ SLUČAJA

Daniela DONAT[1], Sonja LUKAČ[1,2], Ivana BAJKIN[2, 3], Ivana VORGUČIN[2, 4], Viktor TILL[1, 2] and Slađana ZAGORAC[5]

Summary

Introduction. Kallmann syndrome is a genetic disorder marked by hypogonadotropic hypogonadism and anosmia. Patients with Kallmann syndrome have low circulating testosterone levels and low gonadotropin levels, whereas other pituitary hormones are normal. The treatment is based on sex steroid replacement with the aim to restore normal pubertal development and includes attempts to restore fertility by using gonadotropin-releasing hormones. Ultrasound examination of the testicles is a very useful complement to determine and monitor the precise testicular volume, which is an important prognostic factor for future fertility. **Case Report.** At the age of 18, the patient was suspected of having Kallmann syndrome and was referred to an endocrinologist. After three months of testosterone therapy, the patient was sent for an ultrasound of the testicles. The right testicle measured 16 x 6 mm, the left testicle 10 x 5 mm, both with a discrete marginal circular dichroism signal. One year after the first testicular ultrasound, the patient came for a check-up. The right testicle measured 14 x 5 mm, the left testicle 11 x 5 mm, stationary structure. **Conclusion.** The diagnosis of Kallmann syndrome is often delayed, because hypogonadotropic hypogonadism is usually not apparent until puberty, and individuals with anosmia are often unaware of this sensory deficit. In this case, late recognition of the syndrome, as well as late initiation of therapy, did not give satisfactory results.

Key words: Kallmann Syndrome; Ultrasonography; Testis; Hypogonadism; Congenital Abnormalities; Anosmia

Sažetak

Uvod. Kalmanov sindrom se može okarakterisati kao genetski poremećaj obeležen hipogonadotropnim hipogonadizmom i anosmijom. Pacijenti sa Kalmanovim sindromom imaju nizak nivo testosterona sa niskim nivoom gonadotropina, dok su drugi hormoni hipofize normalni. Lečenje se zasniva na zameni seksualnih steroida sa ciljem obnavljanja normalnog pubertetskog razvoja i uključuje pokušaje vraćanja plodnosti primenom hormona koji oslobađaju gonadotropin. Ultrazvučni pregled testisa je veoma korisna dopuna određivanju i praćenju preciznog volumena testisa, što je važan prognostički faktor za buduću plodnost. **Prikaz slučaja.** Posumnjano je da pacijent ima Kalmanov sindrom i sa 18 godina je upućen endokrinologu. Nakon tromesečne terapije testosteronom, pacijent je poslat na ultrazvučni pregled testisa. Desni testis je dimenzija 16 x 6 mm, levi testis 10 x 5 mm, oba sa prisutnim diskretnim marginalnim CD signalom. Godinu dana nakon prvog ultrazvučnog pregleda testisa, pacijent dolazi na pregled. Desni testis je dimenzija 14 x 5 mm, levi testis je 11 x 5 mm, stacionarne strukture. **Zaključak.** Dijagnoza Kalmanovog sindroma se često odlaže jer hipogonadotropni hipogonadizam obično nije očigledan do puberteta, a osobe sa anosmijom često nisu svesne ovog senzornog deficita. U ovom slučaju se pokazalo da kasno prepoznavanje sindroma, kao i kasna primena terapije, nisu dali zadovoljavajuće rezultate.

Ključne reči: Kalmanov sindrom; ultrasonografija; testis; hipogonadizam; kongenitalne anomalije; anosmija

Introduction

Kallmann syndrome (KS) has several synonyms: de Morsier-Gauthier syndrome, olfacto-genital dysplasia, and congenital hypogonadism with anosmia. It is a genetic disorder marked by hypogonadotropic hypogonadism and anosmia [1].

Dr. Aureliano Maestre de San Juan was the first who recognized the association between anosmia and small testicles, whereas Franz Josef Kallmann was the first who described this condition in 1944, suggesting it had a hereditary origin [2].

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, while X-linked, autosomal dominant, and autosomal recessive inheritance patterns were recognized [3].

Congenital hypogonadotropic hypogonadism (CHH) is defined by isolated deficiency or dysfunction of gonadotropin-releasing hormone (GnRH). It

Corresponding Author: Dr Sonja Lukač, Klinički centar Vojvodine, Centar za radiologiju, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: sonja.lukac@mf.uns.ac.rs, viktor.till@mf.uns.ac.rs

Abbreviations
KS – Kallmann syndrome
GnRH – gonadotropin-releasing hormone
MRI – magnetic resonance imaging

is clinically characterized by absent or incomplete development during puberty, resulting in small testicles by the age of 18 years, and infertility in adults. These patients have low circulating testosterone levels with low gonadotropin levels, whereas other pituitary hormones are normal [4].

Also, anosmia has been correlated with GnRH deficiency, since the migration and differentiation of GnRH neurons rely on the formation of the olfactory bulb. Olfactory bulb neurons and GnRH neurons stem from the embryonic nasal epithelium, migrate toward the meninges, and cross the cribriform plate. The GnRH neurons subsequently move to the preoptic area of the hypothalamus guided by olfactory bulb neuron projections. Therefore, defects in the formation of the olfactory bulb and tract may disturb the migration and differentiation of GnRH neurons [3].

Morphological abnormalities of olfactory apparatus in KS are best evaluated by magnetic resonance imaging (MRI). Individuals with KS may present with other malformations including cleft palate, high-arched palate, renal agenesis, sensorineural hearing loss, color blindness, learning disability, and impaired spermatogenesis and fertility [5].

The prevalence of KS varies between 1:10,000 and 1: 80,000 in males, and 1: 50,000 in females, with males being more affected than females (female to male ratio 5:11.5) [6].

The treatment is based on sex steroid replacement with the aim to restore normal pubertal development and includes attempts to restore fertility by administration of GnRH. Timely treatment is important not only to restore metabolic, bone, and sexual balance, but also to mitigate the psychosocial effects associated with KS [7].

Ultrasound examination of the testicles and internal genital organs by an experienced radiologist is a very useful complement to physical examination for precise testicular volume determination and monitoring (during hormone therapy), which is an important prognostic factor for future fertility and

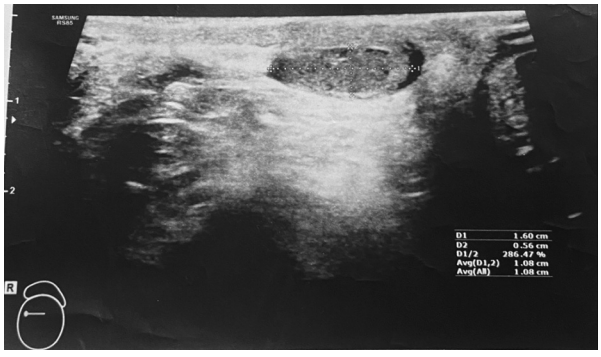

Figure 1. First ultrasound examination - right testicle
Slika 1. *Prvi ultrazvučni pregled – desni testis*

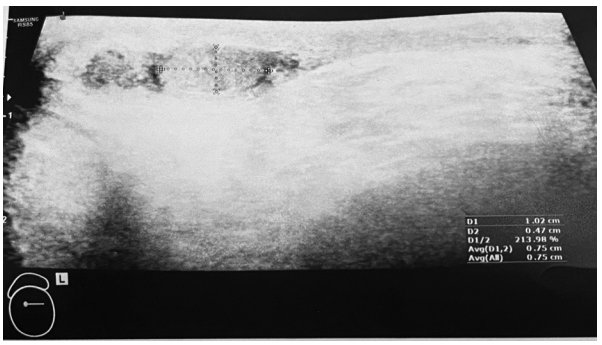

Figure 2. First ultrasound examination - left testicle
Slika 2. *Prvi ultrazvučni pregled – levi testis*

detection of associated abnormalities of the genital tract that may worsen the reproductive function. It also shows the inguinal or intra-abdominal position of one or both testicles in case of ectopy, and this may help guide the therapeutic approach (medical or surgical) in case of cryptorchidism [8, 9].

Case Report

A full-term male patient weighing 4,050 g and measuring 56 cm at birth through a vaginal delivery was diagnosed with bilateral retractile testicles by a pediatric surgeon and was followed until bilateral orchidopexy at the age of five.

After orchidopexy, he visited a pediatrician at the age of seventeen, when he complained of diminished sense of smell. His height and weight were 180.8 cm and 80.5 kg, with left and right testicular volumes of 2 ml, and a penis length -2 SD.

His workup did not show alterations in gonadotropin, testosterone, or estradiol levels: luteinizing hormone < 0.2 mIU/ml (1.7 - 8.6 mIU/ml); follicle stimulating hormone = 0.7 mlU (1.5 - 12.4 mlU/ml); estradiol < 20 pg/ml (7.63 - 42.6 pg/ml); testosterone 0,13 ng/ml. Bone age assessment by X-ray showed a chronological age of 15 years and 6 months.

Skull MRI showed that the patient had hypoplastic olfactory bulbs and shallow olfactory grooves, along with a normal pituitary gland and a normal pituitary stalk. Kallmann syndrome was suspected and the patient was referred to an endocrinologist. He was treated with gonadotropins for a year; after

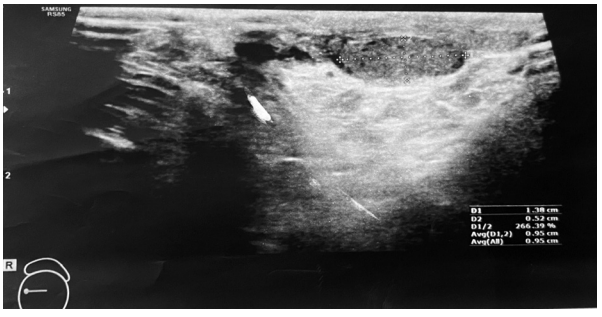

Figure 3. Control ultrasound examination - right testicle
Slika 3. *Kontrolni ultrazvučni pregled – desni testis*

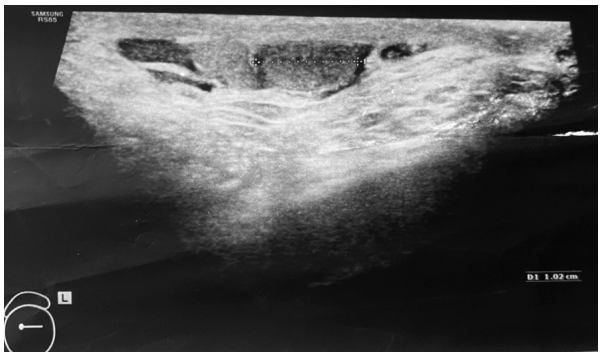

Figure 4. Control ultrasound examination - left testicle
Slika 4. *Kontrolni ultrazvučni pregled – levi testis*

that he started treatment with testosterone cypionate 150 mg/month and the dose was then increased to 250 mg/month.

After three months of testosterone therapy, the patient was sent for an ultrasound of the testicles. The right testicle measured 16 x 6 mm, slight heterogeneous structure, with a discrete marginal circular dichroism signal **(Figure 1)**.

The left testis measured 10 x 5 mm, with discrete heterogeneous structure, also with circular dichroism signal **(Figure 2)**.

One year after the first ultrasound examination of the testicles, the patient came for a check-up. At the time of examination, the patient was on testosterone therapy 250 mg/month. The right testicle measured 14 x 5 mm **(Figure 3)**, the left testicle measured 11 x 5 mm, stationary structure **(Figure 4)**.

Conclusion

Although rare, Kallmann syndrome has a great impact on child and adolescent health, since early diagnosis may trigger multidisciplinary treatment and hormone replacement therapy for hypogonadism and/or help the patient cope with persisting alterations such as anosmia and the risk of infertility. The diagnosis of Kallmann syndrome is often delayed, because hypogonadotropic hypogonadism is usually not apparent until puberty, and individuals with anosmia are often unaware of this sensory deficit. In this case, late recognition of the syndrome, as well as late initiation of therapy, did not give satisfactory results.

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