



# SRY-Positive 46XX Testicular Disorder of Sex Development as a Rare Cause of Male Hypergonadotropic Hypogonadism: A Case Report

## Erkek Hipergonadotropik Hipogonadizmin Nadir Bir Sebebi Olarak SRY Pozitif 46XX Testiküler Cinsel Gelişim Bozukluğu: Olgu Sunumu

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### Abstract

46XX testicular disorder of sex development (DSD) is a rare condition characterized by sexual differentiation disorder with testicular insufficiency. Normal sex development often complicates the diagnosis of this ailment in adults. Patients are usually diagnosed incidentally during infertility research. In this article, we aimed to highlight the hormonal, molecular, and cytogenetic results of an adult male patient diagnosed with 46XX testicular DSD suffering from hypergonadotropic hypogonadism.

**Keywords:** Disorder of sex development; hypergonadotropic; hypogonadism

### Introduction

Disorders of sex development (DSD) are defined as situations where chromosome structure, gonads, or anatomical structure are incompatible with each other. One of these groups of disease, 46XX testicular DSD, was first reported in 1964 (1). The prevalence of 46XX testicular DSD is estimated to be 1 in 20,000 male births (2). Although pubic hair development and penis length post-puberty are normal, these pa-

### Özet

46XX testiküler cinsel gelişim bozukluğu (CGB), testiküler yetmezliğin eşlik ettiği cinsiyet farklılaşma bozukluğu ile karakterize olan nadir bir durumdur. Normal cinsiyet gelişimi, genellikle erişkinlerde bu hastalığın teşhisini zorlaştırır. Hastalar, genellikle infertilite araştırılması sırasında tesadüfen teşhis edilir. Bu yazıda, hipergonadotropik hipogonadizmi olan, 46XX testiküler CGB tanısı almış bir yetişkin erkek hastanın hormonal, moleküler ve sitogenetik sonuçlarını vurgulamayı amaçladık.

**Anahtar kelimeler:** Cinsel gelişim bozukluğu; hipergonadotropik; hipogonadizm

tients have infertility associated with azoospermia (3). 46XX testicular DSD is diagnosed by evaluating clinical, endocrinological, and cytogenetic test results. The most important treatment method, testosterone replacement therapy, is necessary to improve sexual characteristics and sexual desire. In this report, we aimed to document a case of 46XX testicular DSD, who presented with complaints of small testes.

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## Case Report

A 20-year-old male patient visited our outpatient clinic with a complaint of small testes. There was nothing remarkable in his family history and past medical history. Physical examination revealed ill-developed beard, pubic, and axillary hair. Testes were palpated in the scrotum and bilaterally small. Penis length was 10 cm that was smaller as compared to the normal. Patient's height: 168 cm, weight: 65 kg, body mass index: 23 kg/m<sup>2</sup>, vertex-pubis/pubis-heel ratio <1, sexual development compatible with Tanner stage 3, and the patient had no gynecomastia. Laboratory examinations revealed fasting blood glucose, renal function tests, liver function tests, and thyroid function tests were within normal ranges. Endocrinological data were indicated as follows: a serum total testosterone (TT) levels of 275 ng/dL (normal range, 248-836 ng/dL); free testosterone (FT) levels of 5.07 pg/mL (normal range, 8.3-40.1 pg/mL); estradiol levels of 22.14 (normal range, 10-50 mcg/L); follicle-stimulating hormone (FSH) levels of 41.69 IU/L (normal range, 1.5-12.4 IU/L); luteinizing hormone (LH) levels of 38.72 IU/L (normal range, 1.7-8.6 IU/L); prolactin levels of 29.65 (normal range, 4.4-15.2 mcg/L); Adrenocorticotrophic hormone (ACTH) levels of 20.86 ng/L (normal range, 7.2-63.3 ng/L); cortisol levels of 17.99 µg/dL (nor-

mal range, 6.02-18.4 µg/dL); Dehydroepiandrosterone sulfate (DHEAS) levels of 72.37 ug/dL (normal range, 19-407 ug/dL); Growth hormone (GH) levels of 1.08 ug/L (normal range, 0.03-2.47 ug/L); and Insulin-like growth factor 1 (IGF-1) levels of 152.8 ng/mL (normal range, 105-346 ng/mL). Scrotal ultrasonography reflected both testicles in the scrotum, but both were smaller than normal (right testicle: 18x12x9 mm, left testicle: 17x12x9 mm, testicular volume; right 3.9 cc and left 3.2 cc). Both epididymides were of normal size and structure with regular blood supply. Semen analysis indicated azoospermia. The clinical and laboratory findings of the patient are summarized in [Table 1](#). Genetic examinations were conducted with the diagnosis of hypergonadotropic hypogonadism. Karyotype analysis of the patient confirmed a 46XX karyotype ([Figure 1](#)). Fluorescent in situ hybridization (FISH) analysis on the metaphase and interphase chromosomes of 100 cells from 2 peripheral blood cultures explored that the SRY gene was positive. Molecular analysis revealed AZFa SY84, AZFa SY86, AZFb SY127, AZFb SY134, AZFc SY160, AZFc SY254, AZFc SY255 loci deletions. The patient was diagnosed as a 46XX testicular DSD. Genetic counseling was provided. Testosterone replacement therapy was initiated.

Table 1. Clinical and laboratory findings of the patient.

	Patient
Age (year)	20
Height (cm)	168
Body weight (kg)	65
Body mass index (kg/m <sup>2</sup> )	23
Secondary sexual characteristics	Tanner stage 3
Testicular volume	Right 3.9 cc and left 3.2 cc
Gynecomastia	No
Penile length (cm)	10 cm
FSH (mIU/mL)	41.69 (normal range, 1,5-12,4 IU/L)
LH (mIU/mL)	38.72 (normal range, 1,7-8,6 IU/L)
TT (ng/mL)	275 (normal range, 248-836 ng/dL)
FT	5.07 (normal range, 8.3-40.1 pg/mL)
Semen analysis	Azoospermia

FSH: Folliclestimulating hormone; LH: Luteinizing hormone; TT: Total testosterone; FT: Free testosterone.



**Figure 1:** The karyotype confirms the presence of two X chromosomes and the absence of the Y chromosome in the patient.

## Discussion

Several congenital and acquired causes are responsible for the onset of hypergonadotropic hypogonadism. Congenital causes include Klinefelter syndrome, 46XX testicular DSD, FSH-LH receptor gene mutations, mutations resulting in androgen synthesis disorder such as 3 beta-hydroxysteroid dehydrogenase, 17 alpha-hydroxylase, and 17 beta-hydroxysteroid dehydrogenase mutations, cryptorchidism, and myotonic dystrophy. Congenital causes of hypergonadotropic hypogonadism are rare in adults.

46XX testicular DSD is one of the rare causes of hypergonadotropic hypogonadism. Details etiology still remains unknown. However, 3 mechanisms have been proposed regarding pathophysiology. The first is the translocation of the Y chromosome containing the SRY gene on the X chromosome or the autosomal chromosomes, second is X chromosome-dependent mutation/overexpression in testis differentiation genes or mutation/overexpression in autosomal genes (such as the SOX9 gene that differentiates Sertoli cells), and thirdly, Y chromosome mosaicism and mutations in

undefined genes may result in this disease for SRY negative individuals (3). For SRY positive individuals, usually, the appearance and masculinization of the external genitalia are normal. Clinical manifestation is absent, except for the undescended testicle before puberty. Following puberty, pubic hair development and penis size are normal (4). But their testicles are small, and a third of the affected individuals have gynecomastia (5). This form is diagnosed by chromosomal analysis, conducted while investigating infertility and/or small testicles during late adolescence or adulthood. Inadequate virilization of external genitalia immediately after birth help to detect SRY negative form. In most cases, signs of ambiguous genitalia such as micropenis, hypospadias, and cryptorchidism are witnessed (6). Patients with external genital organs with normal male appearance have rarely been reported in the literature.

A combination of clinical, endocrinological, and cytogenetic tests are employed to diagnose 46XX testicular DSD. In most cases, the diagnosis is made during genetic testing for infertility. Hormonal tests reveal hypergonadotropic hypogonadism secondary to

testicular insufficiency. In cytogenetic studies, 46XX karyotype is determined at 550<sup>th</sup> band level. SRY, the gene encoding the sex-determining domain on the Y chromosome, is known to be the most crucial gene for the 46XX testicular DSD. The SRY gene, located on the Y chromosome, plays a prominent role in sex determination. This gene activates the SOX-9 gene that enables the differentiation of Sertoli cells. The R-Spondin1 (RSPO1)-Wnt/ $\beta$ -catenin-FOXL2 signaling pathway, essential for ovarian development, is inhibited by both SRY and SOX-9 (7). SRY has been reported to be positive in approximately 80% of 46XX testicular DSD patients, whereas SRY is found to be negative in approximately 20% of these patients (8,9). The SRY-positive 46XX testicular DSD is generally not hereditary, whereas the SRY-negative 46XX testicular DSD is hereditary.

The differential diagnosis of 46XX testicular DSD includes sex chromosomal abnormalities such as Klinefelter syndrome, 46XX/46XY and 46X/46XY, and congenital adrenal hyperplasia (CAH). Klinefelter syndrome (47XXY) is the most common chromosomal abnormality in males. Classically, clinical features of Klinefelter syndrome include testicular atrophy, infertility, eunuchoidism, and gynecomastia. Contrary to the patients with 46XX testicular DSD, the patients with Klinefelter syndrome have longer stature, delayed speech, learning disorders, and behavioral problems (10). 46XX/46XY: The phenotypic spectrum of the patients with this karyotype varies from normal male or female genital regions to indistinct genital regions to varying degrees. 45X/46XY: Affected individuals are predominantly male and may be seen in short stature, depending on the 45X cell percentage. Chromosome analysis assists in the differential diagnosis between this chromosomal abnormality and 46XX testis DSD (11). Another disorder that should be considered in the differential diagnosis is Congenital Adrenal Hyperplasia (CAH). CAH comprises a group of autosomal recessive inherited disorders attributed to defects in one of the enzymes of steroidogenesis pathway in the adrenal cortex. The most common aberrant enzyme responsible for CAH is 21-hydroxylase (21-OH) deficiency.

Signs of androgen excess during adolescence are evident in the non-classical form of CAH owing to 21-OH deficiency (12). In 46XY CAH patients, completely normal male-looking genitalia is observed, and virilizing type ambiguous genitalia can be perceived (13).

Our patient had normal male phenotype, sparse facial, pubic, and axillary hair, bilateral small testes, and penis size smaller than normal. Primary testicular insufficiency was considered following the consistency of results with hypergonadotropic hypogonadism in endocrinological examinations. Differential diagnosis from Klinefelter syndrome and other sex chromosomal abnormalities were inferred from karyotype analysis. Moreover, the presence of testicles, penis size smaller than normal, absence of ovary, and uterus ruled out the possibility of 46XX CAH.

In the literature, Sreejith et al. and Guneş et al. reported the cases who were admitted with infertility, small-sized testis, and azoospermia and subsequently diagnosed with 46XX testicular DSD and clinical characteristics were comparable to our case. Similar to our case, the SRY gene was also positive in these cases, and deletion was identified in AZFa, AZFb, and AZFc genes (14,15).

The testosterone replacement therapy holds the most prominent treatment modality for 46XX testicular DSD. Testosterone replacement is necessary to augment sexual characteristics and sexual desire. This treatment can develop secondary sex characteristics, including facial and body hair growth, deepening of the voice, muscle and bone accretion, penile enlargement, and pigmentation of the scrotum in patients with incomplete pubertal development. It is also used to rectify symptoms of testosterone deficiency, such as decreased libido, decreased sexual activity, and erectile dysfunction. Testosterone therapy enhances areal and volumetric vertebral and femoral BMD (Bone Mineral Density) and vertebral and femoral bone strength, but its impact on the risk of fracture is unknown. Testosterone is not an approved treatment to reduce the risk of osteoporosis or fractures. It has been documented that total testosterone levels in patients suffering

from cardiovascular disease (CVD) are significantly lower than those without CVD, and every 1 nmol/L increase in testosterone significantly lowers the relative risk for CVD (16). Compared to the control group, the total testosterone level was significantly lower in patients with CVD-related mortality (17). If the patients have symptoms such as psychological disorder, erectile dysfunction, and gynecomastia, a multidisciplinary approach can successfully reduce these problems.

In conclusion, karyotype analysis should be adopted for differential diagnosis of Klinefelter syndrome as well as rare syndromes such as 46XX testicular DSD in patients suffering from hypergonadotropic hypogonadism, presenting clinical symptoms like infertility, small testes, azoospermia, and gynecomastia.

Informed consent was obtained from the patient.

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### Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

### Authorship Contributions

Idea/Concept: Mustafa Can, Melia Karaköse; Design: İlker Çordan; Control/Supervision: Feridun Karakurt, Mustafa Kulaksızoğlu; Data Collection and/or Processing: Mustafa Can, Muhammet Kocabaş; Analysis and/or Interpretation: Mustafa Can, Muhammet Kocabaş; Literature Review: Hatice Çaliskan Burucu; Writing the Article: Muhammet Kocabaş; Critical Review: Melia Karaköse; References and Fundings: Mustafa Can; Materials: Mustafa Can, İlker Çordan.

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