



46,XX Male Syndrome

46,XX Erkek Sendromu

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Abstract

46, XX male syndrome – testicular disorder of sexual differentiation (DSD) is a rare condition characterized by a spectrum of clinical presentations, ranging from ambiguous to normal male genitalia. These cases are diagnosed more easily in childhood. In adults, the diagnosis can be difficult due to the current normal gender development. Here, we report hormonal, molecular and cytogenetic results in an adult male patient with primary hypogonadism who was diagnosed with 46, XX male syndrome in our clinic. *Turk Jem 2013; 17: 46-8*

Key words: 46,XX male syndrome, testicular disorder, SRY gene, primary hypogonadism, chromosomal abnormalities, infertility

Özet

46, XX erkek sendromu-testiküler yetmezlik ile birlikte seksüel farklılaşma bozukluğu, normalden-belirsiz kadar değişen erkek dış genital yapısı ile karakterize nadir görülen bir durumdur. Bu vakalar çocuk yaşlarda daha kolay tanı almaktadır. Yetişkinlerde tanı mevcut normal cinsiyet gelişim nedeniyle zor olabilmektedir. Bu yazıda primer hipogonadizm ile presente olan, kliniğimizde tanı alan, 46,XX erkek sendromlu yetişkin bir erkek olgunun hormonal, moleküler ve sitogenetik sonuçları sunulmuştur. *Turk Jem 2013; 17: 46-8*

Anahtar kelimeler: 46,XX erkek sendromu, testiküler bozukluk, SRY geni, primer hipogonadizm, infertilite

Introduction

46,XX Male Syndrome was first described by De la Chapelle et al. in 1964 (1). In October 2005, in an international multidisciplinary consensus meeting held by Lawson Wilkins Pediatric Endocrine Society (USA) and European Pediatric Endocrinology Community about the management of intersexuality, the title of "46, XX male syndrome" was changed to "46, XX testicular disorder" (2). The incidence of this syndrome is estimated to be 1 in 20,000 to 25,000 male births (3,4). There are 3 clinical phenotypes available: syndromic XX testicular disorder, XX ovotesticular disorder (true hermaphrodites), and isolated XX testicular disorder (5). The aim of this study is to analyze hormonal, molecular and cytogenetic conditions of an adult male who got diagnosed with 46,XX male syndrome in our department.

Case

A 30-year-old male patient was admitted to our clinic with complaints of infertility, erectile dysfunction and decreased sexual

activity. Personal and family history examination showed no significant feature. His height was 161 cm, weight was 80 kg and BMI was 29 kg/m². Physical examination revealed that hair was diminished on facial, axillar and inguinal regions. Testes were in the scrotum, and were bilaterally palpated as small and soft. Penis size was measured as smaller than normal. In the laboratory studies, fasting blood glucose, kidney function tests, liver function tests, thyroid function tests, estradiol (E2), prolactin, progesterone, cortisol, DHEA, growth hormone and ACTH values were within normal limits. FSH level was 26.7 mIU / mL (1.5 to 12.4 mIU / mL) and LH level was 12.4 mIU / mL (1.7 to 8.6 mIU / mL), they were over the limit. Total testosterone level was 0.198 ng / dl (2.8 -8 ng / dl) and free testosterone level was 4.0 pg / ml (12-30 pg / ml); these values were lower than the limits.

Scrotal ultrasonography monitored both testes in the scrotum and their measured sizes were smaller than normal (right testicle was 8x9x14 mm, left testicle was 9x8x15 mm). In pelvic ultrasonography, there were no intra-abdominal mullerian structures. L1-L4 bone mineral density result was consistent with osteopenia with a T

score of -2.3. No sperm cell was observed in spermiogram. With a preliminary diagnosis of hypergonadotropic hypogonadism, genetic and cytogenetic studies were done. In patients' cytogenetic analysis, 46,XX male karyotype was detected. Molecular studies of the patient showed that he carried the SRY gene region, but in other regions the AZFa, AZFb, AZFc, AZFd deletions were detected as well. In Y micro-deletion tests the deletion was detected in all regions examined except SY133, SY14 (SRY) and internal controls. Prostate specific antigen level was found to be within normal limits and testosterone replacement therapy was administered to the patient.

Discussion

Genetic causes resulting in primary hypergonadotropic hypogonadism are rarely seen in adults. In the literature, 150 cases of 46,XX testicular disorder patients have been reported up to 1996, yet this number decreased to 100 cases between 1996 and 2006 (6).

It is thought that the translocation of TDF (testis determination factors) from Y chromosome to X chromosome occurring as a result of unequal crossing between X and Y chromosomes during paternal meiosis causes this syndrome (7).

In adults, the diagnosis of this disorder is difficult due to the normal gender development in progress. In about 80% of these individuals, even though normal pubic hair growth after puberty and normal penis sizes are detected, infertility is observed resulting in small testicles and azoospermia. Gynecomastia can be detected in about one-third of affected individuals. Suspected genitalia at birth is observed in 20% of these individuals. The gender role and social gender identity of these individuals are reported as male (8). This syndrome gets diagnosed by the evaluation of a combination of clinical signs, endocrinological tests and cytogenetic tests. The results of endocrinological tests show hypergonadotropic hypogonadism as a result of testicular failure. In cytogenetic studies, 46,XX karyotype is determined at the 550th band level. SRY (Sex-Determining region on the Y) gene is evaluated in FISH or PCR studies.

SRY gene is located on the Y chromosome and has an important role in determining gender. This protein activates the SOX-9 gene which induces the differentiation of sertoli cells. Both SRY and SOX-9 genes inhibit RSPO-1 (R-spondin-1) -Wnt-4- β -catenin-FOXL2 signaling pathway that is essential for ovarian development (9). After the analysis of the SRY gene, 46,XX male patients are divided into two clinical groups as SRY positive and SRY negative patients. SRY gene is positive in approximately 80% of these individuals and negative in 20%. SRY-positive individuals have normal male genitalia, azoospermia, small testes and they are usually diagnosed during adulthood infertility research (10,11).

In general, SRY-positive 46,XX testicular disorder is not hereditary. It is due to the abnormal change between the Y and X chromosomes resulting in the presence of SRY gene on the X chromosome and infertility. When the SRY gene is translocated to another chromosome, the fertility is preserved and autosomal dominant inheritance occurs. Syndromic type 46,XX testicular disorder is characterized by palmo-plantar keratosis and a predisposition to

squamous cell carcinoma of the skin and it is diagnosed by the presence of R-Spondin1 mutation (9,11).

Most of the individuals in SRY-negative group show ovotesticular sexual development. In patients with ovotesticular sexual development disorder, gonads have both ovarian and testicular tissue, while in patients with testicular sexual development disorder both gonads have only testicular tissue. The diagnosis of SRY-negative testicular disorder of sexual development is often made in childhood - during the examination about suspicious genitalia and gynecomastia (12,13).

In the differential diagnosis of 46,XX testicular disorder, sex chromosome abnormalities causing primary testicular failure (hypergonadotropic hypogonadism) such as Klinefelter's syndrome, 46,XX/46,XY and 46,X/46,XY should be considered. Klinefelter's syndrome (47, XXY and variants) is the most common chromosomal abnormality among men and it is characterized by abnormal sexual development at puberty, small testes, specific body structure and the absence of secondary sex characteristics. In this syndrome, infertility - caused by hormonal and spermatogenic testicular failure-, low testosterone levels, erectile dysfunction and low bone mineral density are observed (14).

In SRY-positive 46,XX testicular disorder, Klinefelter's syndromes' classic phenotypic characteristics like onychoid body structure are not seen very often. Also, learning disorders and behavioral problems are observed in patients with Klinefelter's syndrome, which is not present in patients with 46,XX testicular disorder (6).

Individuals with 46,XX/46,XY chimerism may emerge as true hermaphrodites and may vary from normal male to normal female based on the relative ratio of XX and XY cells. In males having 45,X/46,XY karyotype, short stature can be seen based on the percentage of 45,X cells. It can't be distinguished from 46,XX testicular disorder in clinical examination. However, chromosome findings are diagnostic (15).

Another disorder that should be considered for differential diagnosis is the congenital adrenal hyperplasia (CAH). With the incidence of approximately 1/16000, CAH is a disorder of excessive androgen production in the prenatal and postnatal periods due to the disorder of genes that are responsible for the production of enzymes involved in adrenal steroidogenesis. The most common enzyme defect that causes CAH is 21-hydroxylase (21-OH) deficiency. Non-classic or late-onset congenital adrenal hyperplasia due to a lack of 21 - hydroxylase usually comes out with signs of excess androgen in later stages of life, not with suspicious genitalia at birth (16).

Classic CAH in the 46,XX individuals is associated with the behavioral and sexual organ masculinization. According to the external genitalia and changing spectrum of virilization, phenotype can vary from female looking genitalia to male looking genitalia missing both scrotal gonads (Prader stages 2-5) (17).

The differential diagnosis of our case must be made with complete-severe 46,XX 21-hydroxylase deficiency cases of patients showing male virilization. These patients have normal size penises and scrotum, but no testicles exist inside scrotum. The ovaries and uterus are present. Vagina may merge with urethra. These patients don't have ambiguous genitalia and they are diagnosed as boys with undescended testes. The diagnosis of CAH can't be made

without the findings of salt loss. CAH patients showing complete virilization have a high risk of late diagnosis. Screening program for CAH in the neonatal period is important not to bypass these errors. 46,XY Congenital Adrenal Hyperplasia (CAH) patients may have completely normal looking male genitalia with an electrolyte imbalance or virilizing type ambiguous genitalia (18).

In our case, normal male phenotype, infertility, bilateral gynecomastia, erectile dysfunction, lack of intra-abdominal müllerian organs, and hormone tests showing primary hypergonadotropic gonadism lead us to the diagnosis of primary testicular failure. Having small testes and other findings were similar to Klinefelter syndrome. Yet differential diagnosis from Klinefelter's syndrome and other sex chromosome abnormalities was made through karyotype analysis.

Nowadays, in hormonal induced male infertility, the importance of laboratory support in evidence-based treatment practices is undeniable. It is possible to trigger the production of testosterone and spermatogenesis by replacing the lack of GnRH, LH and FSH hormones.

46,XX karyotype testicular disorder is a rare sex chromosome abnormality which is difficult to diagnose in adults. But if these individuals are not diagnosed and left untreated, testosterone deficiency results can be seen. In the treatment of patients with 46,XX testicular failure, multidisciplinary approach should be considered. In these patients, viewing gonads, measurements of bone density and blood tests should be done regularly and these patients should be followed by an endocrinologist for life. Psychological support is an important part of the holistic approach. In conclusion, in cases of hypergonadotropic hypogonadism who presented complaints of azoospermia and infertility, karyotype analysis should be performed in the differential diagnosis of these rare syndromes as well as in the differential diagnosis of Klinefelter's syndrome and mosaic forms.

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