**46,XX TESTICULAR DISORDER OF SEX DEVELOPMENT. CASE REPORT**

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**Summary.** OBJECTIVE: We present a case of X-Y translocation with male phenotype (46,XX testicular disorder of sex development) and review the literature.

METHODS: Disorders of sex development with mismatch of genetic, gonadal and phenotypic sex are quite rare, and some are due to genetic or chromosomal abnormalities. The karyotype was investigated by a cytogenetic study of peripheral blood (phytohemagglutinin-stimulated lymphocyte culture over 72 hours). G-banding analysis of 25 metaphases showed a 46,XX chromosome constitution (46 chromosomes with XX sexual composition). Fluorescence in situ hybridization (FISH) analysis with probes for X centromeres and the sex-determining region of the Y chromosome (SRY) (testis-determining factor gene) showed two X chromosomes. The analysis also showed the SRY signal in the telomeric region of the short arm of one of the chromosomes.

RESULTS: In recent years, a number of other genes involved in disorders of sex development in animals and humans have also been identified.

Genetic defects in the peptide hormone receptors, members of the steroid receptor superfamily, and other transcription factors, as well as any of a series of enzymes and cofactors involved in steroid biosynthesis can cause abnormal determination and differentiation.

CONCLUSIONS: Although chromosomal abnormalities are rarely present in patients with apparently normal external genitalia, they should be considered in urology consultations by adolescents and adults, particularly in the investigation of gynecomastia or infertility.

**Keywords:** Disorder of sex development. Translocation. SRY.

**Resumen.-** OBJETIVO: Presentamos un caso de translocación entre cromosomas X e Y, con fenotipo masculino (46,XX testicular DSD) y revisamos la literatura.

MÉTODOS: Los trastornos de la diferenciación sexual en los que no hay correspondencia entre los sexos genético, gonadal y fenotípico son muy raras, y algunos son debidos a alteraciones genéticas o cromosómicas. Se efectuó estudio citogenético, realizando cariotipo en sangre periférica (cultivo de linfocitos de 72 horas de duración estimulados por fitohemaglutinina). Las 25 metáfases analizadas con bandas G muestran una constucción cromosómica de 46,XX (46 cromosomas con constitución sexual XX). El análisis también muestra la señal para SRY en la región telomérica del brazo corto de uno de los cromosomas.

RESULTADOS: En los últimos años se han identificado varios genes a parte del SRY, en animales y en humanos que intervienen en los trastornos de la diferenciación sexual. Los defectos genéticos en los receptores de las hormonas pépticas, los miembros de la superfamilia de los receptores esteroideos y otros factores de transcripción, así como cualquiera de una serie de enzimas y cofactores que intervienen en la biosíntesis de los esteroides pueden inducir una determinación y una diferenciación anómala.

**Keywords:** Desorden de desarrollo sexual. Translocación. SRY.
INTRODUCTION

Undifferentiated gonad has the unique characteristic of having the potential to form two organs: testes and ovaries.

To date, more than fifty genes that regulate sex differentiation processes have been identified in autosomes and sex chromosomes. These genes encode transcription factors, gonadal steroids, peptide hormones, and tissue-specific receptors (1).

CASE REPORT

A 20-year-old patient with a personal history of circumcision under general anesthesia at age 6 and tonsillectomy and a family history (father) of left-sided orchiectomy for testicular seminoma tumor 10 years earlier presented for small testes and penis.

The physical examination showed a circumcised penis of normal size, with orthotopic meatus, but firm, very small testes. Palpation showed ductus deferens of normal appearance, and pubic hair was of normal distribution. The patient had no beard or gynecomastia; height was 169 cm and weight, 76 kg.

The routine laboratory workup showed normal complete blood count and biochemistry, testosterone 2.3 ng/mL (normal range, 2.8-8), prolactin 24.5 ng/mL (4-15.2), luteinizing hormone 16.5 mIU/mL (1.7-8.6), follicle-stimulating hormone 27.9 mIU/mL (1.5-12.4), and estradiol 24.8 pg/mL (11-44). Several subsequent analyses confirmed elevated gonadotropins; testosterone remained near the lower limit of normal.

The karyotype was investigated by a cytogenetic study of peripheral blood (phytohemagglutinin-stimulated lymphocyte culture over 72 hours). G-banding analysis of 25 metaphases showed a 46,XX chromosome constitution (46 chromosomes with XX sexual constitution). Fluorescence in situ hybridization (FISH) analysis with probes for X centromeres and the sex-determining region of the Y chromosome (SRY) (testis-determining factor gene) showed two X chromosomes. The analysis also showed the SRY signal in the telomeric region of the short arm of one of the chromosomes. The findings corresponded to a male phenotype with two X chromosomes, one of which resulted from an unbalanced translocation between the short arms of the X and Y chromosome, resulting in an X derivative with SRY at Xp22.3.

The patient and his family were informed of the genetic abnormality; the patient expressed that his main concern was testes size, because erections and ejaculations were normal. An abdominal and pelvic computed tomography scan revealed no other abnormality; a spermogram showed azoospermia.
The patient requested testicular prostheses to improve the appearance of the genitalia. During the surgery, normal morphology of the testes and epididymis was confirmed, the testis was measured (longitudinal diameter of 11 mm), and right testicular biopsy (Figure 3) was performed. Bilateral testicular prostheses were implanted outside the tunica vaginalis testis (Figure 4) using a low inguinal approach and preserving the testes.

The histological results showed testicular parenchyma with marked fibrosclerosis of most of the seminiferous tubules, alternating with other tubules lined only with Sertoli cells. Leydig cell hyperplasia was also observed (Figure 5).

DISCUSSION

Over the last 35 to 40 years, genetic and molecular studies carried out in patients with intersex conditions have contributed to a better understanding of the sexual differentiation process.

Because the old nomenclature used to refer to disorders of sex development (eg, intersex, hermaphroditism, pseudohermaphroditism) was unhelpful, confusing, and stigmatizing or pejorative for patients and their families, a consensus statement was issued, although not entirely successfully, to amend the old nomenclature and replace it with a generic definition that describes a congenital condition (known at birth or perhaps before birth) of a mismatch or lack of agreement between the genetic, gonadal-hormonal and phenotypic sex (2). The English literature uses the acronym DSD (disorder of sex development) along with the karyotype to define the type of DSD. In Spanish and Latin American literature, the acronym ADS (anomalías de diferenciación sexual) has also been used (3).

The genetic sex-determination cascade includes the SRY gene, identified in the early 1990s by McElreavy SRY as a small single exon gene that induces differentiation of the undifferentiated gonad to testis. In recent years, a number of other genes involved in disorders of sex development in animals and humans have also been identified. For instance, SOX9 was originally identified in individuals with skeletal malformations and dysplasia or campomelic syndrome, as well as in 46,XX and XY DSD individuals. DAX-1 (congenital adrenal hyperplasia gene), WT1 (Wilms tumor gene) and SF1 (steroidogenic factor 1) are also involved in the sex-determination cascade (1, 4).

Genetic defects in the peptide hormone receptors, members of the steroid receptor superfamily, and other transcription factors, as well as any of a series of enzymes and cofactors involved in steroid biosynthesis can cause abnormal determination and differentiation (1).

Hormone production by the embryonic testis is essential for male sex differentiation: anti-müllerian hormone (AMH) produced by Sertoli cells induces regression of the müllerian ducts, whereas androgens synthesized by Leydig cells cause development of the Wolffian ducts (epididymides, vas deferens, seminal vesicles, and testicular descent). If the gonad develops as ovaries, the Wolffian ducts will regress and the müllerian ducts will develop as Fallopian tubes, uterus, and upper vagina.

Genital abnormalities present in 1 of every 4500 births. Some of these abnormalities are caused by chromosomal abnormalities. When mutations in the genes responsible for these processes are nonfatal, they can lead to sex reversal (5). There are two well-defined ty-
pes of complete sex reversal: 46,XX men, in whom bilateral testes and male phenotype develop, and 46,XY women, who develop bilateral streak gonads instead of testes and consequently female phenotype, despite the Y chromosome. The XX male syndrome was first described by De la Chapelle in 1964; the syndrome appears in one of every 20,000 newborn males (6) and is responsible for 2% of all cases of sterility in men (7).

Many patients (85%) have normal phenotype at birth and are usually diagnosed when consulting for hypogonadism, gynecomastia, or infertility (4).

The mechanism implicated in testicular DSD is translocation between the X and Y chromosome during paternal gametogenesis, specifically in the short-arm segment of the Y chromosome. Abnormal X and Y translocation involving the SRY gene during meiosis with chromosome X inactivation causes 80% to 90% of XX males (7,8). The amount of DNA material involved in the exchange is variable; however, in general, the greater the amount of Y chromosome DNA present, the more masculinized the phenotype will be (1).

Testicular XX males can be divided into three groups: a “classic” group with male phenotype; another group with ambiguous genitalia; and a third group with true hermaphroditism. Around 300 case reports (mostly individual case studies) from the first group have been published. Of these individuals, 90% of them have Y chromosomal material including the SRY gene located at the end of the short arm of the paternal X chromosome. Azoospermia was common among all these patients, probably caused by the absence of the AZF region on the Y chromosome (9).

The SRY gene has been established as necessary and sufficient for sex determination on the Y chromosome in mammals. This belief was held because XX(SRY+) subjects were men with male genitalia, whereas XX(SRY-) subjects had ambiguous genitalia. The presence of SRY is often associated with male genitalia, whereas the absence of SRY is usually associated with ambiguous genitalia. Nevertheless, there are a few XX(SRY+) subjects with ambiguous sexual characteristics and, therefore, another Y chromosome gene contributing to complete male sex differentiation has been postulated. In a small number of SRY+ cases with ambiguous genitalia, there is a small Y fragment located on inactive X in most metaphases (7,8).

Slaney (10) reported a family of 46,XX(SRY-) individuals with true hermaphroditism, one with male genitalia and three with ambiguous genitalia, and proposed that the genetic defect in 46,XX individuals born of normal parents is most likely due in part to an autosomal dominant mutation with different phenotypes, depending on the extent of penetrance.

Temel (11) described the rare case of a family with nine members who were SRY- and had no SOX9 duplications or mutations (five cases of testicular DSD and four cases of ovotesticular DSD) with predominance of male phenotype.

However, the observations made by Sharp (12) suggest that incomplete masculinization in cases of X/p translocation is probably caused by the interruption of normal SRY expression by the “position effect” resulting from the new chromosome arrangement, rather than by X inactivation.

Diagnosis is based on clinical findings, an endocrine study, and cytogenetic testing (13). Disorders of sex development characterized by a 46,XX karyotype (46,XX testicular DSD) include external male genitalia ranging from normal to ambiguous (penoscrotal hypospadias with or without chordae), two testes, and azoospermia. Müllerian structures are absent. After puberty, around 80% of individuals with 46,XX testicular DSD present small testes, gynecomastia and sterility due to azoospermia, but normal pubic hair. The testes are small and soft, but may become more firm with age. Cryptorchidism is present in 15% and anterior hypoplasias in around 10%. Endocrine testing normally reveals hypergonadotropic hypogonadism secondary to testicular failure (7,13). Cytogenetic testing reveals 46XX. Approximately 80% of 46,XX testicular DSD individuals are SRY+ (SRY encodes sex determination in the testes), and the investigation is usually based on FISH or polymerase chain reaction amplification of the SRY gene; around 20% of 46,XX testicular DSD patients are SRY- (7,13).

Treatment consists of correcting the hormonal deficiencies and resembles that of other processes characterized by low testosterone levels. If gynecomastia is present and does not remit with hormone therapy, plastic

![FIGURE 5. Severe testicular atrophy with Leydig cell hyperplasia. Masson trichrome, x200.](image-url)
surgery of the breasts may be necessary. Additional surgical procedures may sometimes be needed to improve the appearance of the external genitalia (surgery for hypospadias, cryptorchidism, etc.) or, as in our case, implantation of a testicular prosthesis. In some cases, sex reassignment and genital reconstruction may be necessary. In many cases, patients and their families may require psychological support.

SRY + 46,XX DSD is not usually hereditary and is the de novo result of abnormal Y and X chromosome crossover that leads to the presence of SRY on the X chromosome and to infertility. When the SRY gene is translocated to another chromosome or when, on rare occasions, fertility is preserved, autosomal dominant inheritance can be observed. The mode of SRY inheritance is unknown. Prenatal diagnosis of SRY+ is possible (13). Prenatal diagnosis may also be possible in some cases of DSD. In particular, the use of ultrasound during pregnancy may reveal abnormalities of the fetal genitalia. After week 19, the presence of a uterus is a key finding of the prenatal assessment. The association of genetic testing (chorionic villi biopsy, amniocentesis, and umbilical cord samples) that includes chromosome analysis and FISH of the SRY gene, along with abnormal hormone, enzyme, and metabolite results from the amniotic fluid and maternal serum may aid the diagnosis in many cases (14), allowing fetal treatment to be implemented in selected cases.

CONCLUSIONS

Although chromosomal abnormalities are rarely present in patients with apparently normal external genitalia, they should be considered in urology consultations by adolescents and adults, particularly in the investigation of gynecomastia or infertility.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


