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Erectile function in SRY positive 46,XX males with normal phenotype

Metin Yiğman[1], Semih Tangal[1], Ahmet Hakan Haliloğlu[1], Gamze Sinem Çağlar[2]

[1]*Ufuk University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[2]*Ufuk University Faculty of Medicine, Department of Obtetrics and Gynecology, Ankara, Turkey*

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Corresponding author
Metin Yığman
Ufuk University Faculty of Medicine
Dr. Ridvan Ege Hospital
86-88 Mevlana Boulevard
Ankara, Turkey
phone: +90 5358 281 607
m.yigman@hotmail.com

Introduction The 46,XX male syndrome is a rare disorder of sex development and has two different forms, depending on the sex-determining region's presence on the Y chromosome (SRY) gene. The SRY positive 46,XX males are usually diagnosed during infertility workup. We evaluated the erectile function of 46,XX SRY positive males and compared it with healthy males.

Material and methods Ten patients with azoospermia and 46,XX SRY positive disorder who referred to a urology clinic with infertility were analyzed retrospectively. Controls were chosen from healthy males at similar ages. The physical examination was performed, and serum hormones were obtained at admission. The clinical assessment of erectile dysfunction was evaluated by the International Index of Erectile Function (IIEF) questionnaire.

Results There was no statistically significant difference between the two groups in terms of age, serum prolactin, luteinizing hormone (LH) levels and IIEF scores (P >0.05). In 46,XX males, serum follicle-stimulating hormone (FSH) levels were significantly higher, and total testosterone levels and testicular volumes were found to be significantly lower when compared to controls (p <0.001, p <0.05, p <0.01, respectively).

Conclusions This study indicates that these males' erectile function is similar to those of 46,XY males.

Key Words: erectile dysfunction ‹› infertility ‹› azoospermia ‹› 46,XX disorders of sex development ‹› genes ‹› sex-determining region on Y chromosome

INTRODUCTION

The 46,XX male syndrome is a rare disorder of sex development (DSD), occurring in 1:20,000 newborn males [1]. The first 46,XX male DSD was reported in 1964 by de la Chapelle [2]. Up until today, less than 300 cases have been reported.

There are two different forms of 46,XX DSD, depending on the presence of SRY (sex-determining region on Y chromosome) gene [3]. Even if different mechanisms are proposed to explain this syndrome, in 90% of these cases, the SRY is translocated to X chromosome or autosomal chromosomes [4]. As the SRY gene has the significant role in encoding testis determining factor (TDF), testicular development occurs, and these cases have a normal male phenotype in SRY positive form of the disorder (SRY positive, 46,XX male syndrome) [5, 6]. The SRY positive 46,XX males are the most common phenotype, also known as the classic form presenting as normal males with small testes [7]. However, as the AZFa, AZFb and AZFc regions of the Y chromosome's long arm are lacking, these patients are often infertile [8]. This classic phenotype 46,XX males are usually diagnosed during infertility workup [7]. As long as they have no fertility desire, these patients' only problem with male phenotypes would be their erectile capacity.

Another spectrum of this syndrome is known as SRY negative 46,XX testicular DSD that presents with incomplete masculine phenotype. SRY negative phenotypes (10%) are characterized as ovotesticular DSD, where ovaries and testes are present in the same individual. In SRY negative DSD form, the mechanism of testicular tissue differentiation is still unknown.

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Masculinization varies among these individuals [4, 9, 10, 11].
In the literature, numerous authors have written about the clinical, molecular, and cytogenetic findings of SRY positive and negative forms of the syndrome. For the first time in the literature, we evaluated the erectile function of 46,XX SRY positive DSD males and compared them with healthy males.

MATERIAL AND METHODS

In our clinic, the infertile males are systemically assessed by semen analysis and serum hormone testing. During the infertility workup, chromosome analysis in the blood is performed in males with a sperm count less than $10x10^6$/ml. In this study, the records of 46,XX males who have infertility are documented.
Blood samples were obtained at admission for serum hormones. Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), total testosterone (total-T) were determined. Serum FSH, LH, E2, PRL, and total-T, were measured with electrochemiluminescence assays (ELECYS 2010 HITACHI, RocheDiagnostic, Germany). The intra and inter assay coefficients of variation (CV) were <1.9% and <4%, respectively, for all assays performed.
The physical examination, of all cases and controls, were recorded. Prader orchidometry was used for testis volume evaluation, and the volume of both testes were recorded. Semen samples from patients were obtained by masturbation after 2–5 days of sexual abstinence and stored in sterile containers. According to World Health Organization criteria, basic sperm parameters (concentration, motility and morphology) were evaluated in all samples (WHO, 2010).
The clinical assessment of erectile dysfunction of these cases was evaluated by the International Index of Erectile Function (IIEF) questionnaire. For the diagnosis of erectile dysfunction questions, 1, 2, 3, 4, 5 and 15 were considered (5 points for each question). When the total score of these six questions is more than 26 points, the patient has no erectile dysfunction. When the score is between 22 and 25, there is minimal dysfunction. Scores between 17 and 21 indicate mild dysfunction and 11 and 16 moderate dysfunction. If the scores are from 0 to 10, then the patient has severe erectile dysfunction.
Controls were chosen from healthy males at similar ages. The IIEF scores of controls are also documented. In all males diagnosed with erectile dysfunction, the related vascular, neurologic, psychological and hormonal causes are investigated. All data were retrospectively reviewed and evaluated.

Statistical analysis

Collected data were analyzed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normal or not, was determined by the Shapiro Wilk test. Descriptive statistics for continuous variables were shown as mean ± standard deviation or median (minimum-maximum). Student's test compared the mean differences between groups. Otherwise, Mann-Whitney U test was applied for the comparisons of the median values. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, between 2008 and 2019, 9665, patients were admitted to our andrology clinic. Among these cases, records of azoospermia were analyzed to document 46,XX SRY positive cases. Finally, ten patients were found to have azoospermia and 46,XX SRY positive karyotype during the mentioned period. These men's mean ages were 27.9 ±3.5 years in cases and 27.2 ±3.6 years in controls (Table 1). All 46,XX male DSD cases and all controls have completely masculinized phenotype, normal male internal and external genitalia. At the urological examination, testicular volumes (right, left and total) of cases were significantly smaller than controls ($p < 0.05$, Table 1). The hormone profiles of 46,XX SRY positive men showed hypergonadotrophic hypogonadism with significantly higher FSH levels and significantly lower testosterone levels ($p < 0.001$* and $p = 0.02$, respectively; Table 1).
Only two (20%) men in each group had minimal erectile dysfunction in cases and controls. When the cases and controls are compared for the IIEF scores, no significant difference was found ($p > 0.05$).

DISCUSSION

One of the rare genetic forms of primary hypergonadism is 46, XX SRY positive males. In previous case series, high levels of gonadotropins and low total testosterone levels were reported by different authors [3, 12]. Our cases' hormone profile also supports this data that these cases have lower testosterone levels and high levels of gonadotropins. On the contrary, others reported average levels of gonadotropins and testosterone [9, 13].
While patients' clinical symptoms often show some degree of heterogeneity [4], usually, the development of genitalia is normal, and masculinity signs are apparent in SRY+ patients. There is no abnormality

Table 1. *The age, hormone levels, testis size and International Index of Erectile Function (IIEF) scores*

	46XX males (n = 10)	Control (n = 50)	p
Age (years) mean ±sd	27.9 ±3.5	27.2 ±3.6	NS
FSH (mIU/ml) median (min-max)	12.2 (7.3–28.3)	5.4 (3.1–11.2)	<0.001*
LH (mIU/ml) mean ±sd	7.6 ±4.0	4.7 ±4.7	NS
Total testosterone (ng/ml) median (min-max)	2.6 (1.2–4.9)	6.0 (1.6–10.4)	0.02*
Prolactin (mIU/ml) mean ±sd	7.1 ±3.0	6.0 ±3.9	NS
Right testicular volume (ml) median (min-max)	15 (12–20)	20 (15–25)	0.01*
Left testicular volume (ml) median (min-max)	15 (12–20)	20 (15–25)	0.004*
Total testicular volume (ml) mean ±sd	29.4 ±4.9	39 ±6.5	0.002*
IIEF scores median (min-max)	28.5 (24–30)	29 (21–30)	NS

*p <0.05 statistically significant; NS – not significant; sd – standard deviation; FSH – follicle-stimulating hormone; LH – luteinizing hormone

in the development of penis and sex psychology and erection and ejaculation, and there are almost no significant positive signs except cryptorchidism before puberty. It is challenging to find SRY+ male DSD patients before puberty, often incidentally found by chromosome check for infertility or low testicle development.

In all cases of this study, the reason for admission was infertility. At initial evaluation, small testes at the physical examination were the only remarkable finding. All the data about SRY positive 46,XX DSD patients in the literature indicate reduced testicular volumes, as in our series [3, 9, 12, 13]. Azoospermia related infertility is an indication for chromosome analysis. Otherwise, these cases cannot be diagnosed.

The mechanism of action of testosterone is linked to vascular endothelium, where it regulates the production of nitric oxide through the stimulation of nitric oxide synthase and the formation of cyclic guanosine monophosphate. Therefore testosterone affects erection. It increases penile rigidity and prolongs erectile response [14].

Hypogonadism and erectile function have a known association, and therefore, normalization of testosterone can improve the quality of erections. According to the European Association of Urology (EAU), plasma testosterone concentrations <8 nmol/L are considered abnormally low and require substitution. For higher concentrations, the relationship between circulating testosterone and sexual performance is vague. According to the American Urological Association, testosterone concentration should be checked in all men with erectile dysfunction (ED) in order to determine if testosterone deficiency, defined as a total testosterone level of <300 ng/dl along with hypogonadism symptoms, occurs. Also, men with ED and testosterone deficiency, who are considering treatment for ED with phospohodiesterase type 5 (PDE5) inhibitors, should be informed that these drugs may be more effective if combined with testosterone therapy.

This is the first study in the literaure evaluating erectile function by an internationally accepted standard form. The IIEF scores of 46,XX SRY positive males were similar to 46,XY males.

We see that the results of our study are compatible with the literature. In the 46XX male case reports and reviews published by Terribile et al., 27 of 30 patients evaluated for ED in these cases presented in the literature have reported normal erectile functions [15]. Ferlin et al. evaluated sexual dysfunction in patients with Klinefelter syndrome, the most common genetic form of primary hypogonadism. In the Klinefelter syndrome group, sexual desire, sexual satisfaction and general satisfaction were positively correlated with testosterone levels; on the contrary, there was no relationship between erectile function, orgasmic function and testosterone levels. As a result of their studies, they found that individuals with Klinefelter syndrome have a wide variety of neurocognitive, psychosexological, and relational problems, and ED symptoms were mainly associated with these disorders [15]. On the other hand, Yoshida et al. found no significant difference in the incidence of sexual dysfunction, including sexual desire, between men with Klinefelter syndrome with normal total testosterone levels and men with Klinefelter syndrome with decreased total testosterone levels [16].

The results of our study may appear inverse to the relationship between hypogonadism and erectile dysfunction. One of the reasons is that at adolescence, in classic phenotype 46,XX DSD, testosterone levels are normal, but in adults, low levels are usually detected reflected as hypergonadtrophic hypogonadism [5]. In the relatively young men (mean age 27.9 years) presented here, hypergonadtrophic hypogonadism is detected without sexual problems, but the erectile function needs to be re-evaluated in advanced ages. Another reason may be that patients have cognitive deficits about normal erections. The fact that the patients presenting complaint is infertility indicates that they have erectile functions. However, the grading of erectile capacities is controversial. Our study's limitation was that these patients were not questioned again after testosterone replacement, which is because the primary complaint was infertil-

ity and the inability to have a child and the absence of reapplication. With regards to fertility, options are limited to artificial insemination or in vitro fertilization using donor sperm or opting for adoption.

CONCLUSIONS

The 46,XX DSD is a rare condition for which data is limited to presented literature cases. This study contributes to previous literature reporting erectile function in this rare disorder. We infer that, in 46,XX DSD, erectile dysfunction is neither a complaint nor a reason for admission. Therefore, the only chance of diagnosis is at admission for infertility. As a result, even if the hormonal profile is altered, an erectile function of 46,XX SRY positive males is similar to 46,XY males.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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