46, XY DISORDER OF SEXUAL DEVELOPMENT WITH AMBIGIOUS FEMALE EXTERNAL GENITALIA: A CASE REPORT

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Abstract

Disorder of Sexual Development (DSD) is a group of congenital conditions with atypical development of sex at chromosomal, gonadal or anatomic level. Genetic males with DSD (46 XY DSD) can present with female external genital phenotype, ambiguous, or a micropenis. It is caused by incomplete intrauterine masculinization with or without the presence of Müllerian structures. It results either from decreased synthesis of testosterone or DHT or from impairment of androgen action. Herein, we report a case of a 13-year child raised as female with hoarseness of voice and gradual enlargement of clitoris with hormonal assessment not suggestive of either 5 Alfa Reductase deficiency, Congenital Adrenal Insufficiency Syndrome or 17β-Hydroxysteroid Dehydrogenase deficiency

INTRODUCTION

Introduction

DSD are collection of rare conditions with atypical genitalia in the newborn period or as delayed puberty in an adolescent. They are generally characterized by an abnormality of the chromosomal, gonadal or phenotypic features that typically define sex development.(1) Reported incidence of DSD is 1:4,500 births,(2) whereas a concern about the development of the external genitalia may, however, exist in one in 300 newborn infants(1). Sometimes it is difficult to reach the final diagnosis of the DSD. Herein, we report a case of a 13-year child raised as female with hoarseness of voice and gradual enlargement of clitoris. Her hormonal assessment was neither in favor of 5 Alfa Reductase deficiency, Congenital Adrenal Insufficiency Syndrome nor 17β-Hydroxysteroid Dehydrogenase deficiency. Therefore, we feel this case to be reported.

CASE REPORT

A 13-year child raised as female was brought to urology department with hoarseness of voice and gradual enlargement of clitoris. There was no menarche till the date. She had no significant past medical, surgical and family history. She had no history of parental consanguinity marriage.

On physical examination, there was small size phallus with perineal hypospadias and open urethral plate ventrally, scrotum not developed with impalpable bilateral testes, vaginal canal not seen and male pattern pubic hair growth (Figure1). Breasts were Tanner stage I. Serum hormonal levels were like Estradiol (E2) 32.96 (5.37-65.9 pg/ml), Follicle Stimulating Hormone (FSH) 62.60 mIU/ml, Leutinizing Hormone (LH) 39.4 (1.5-9.3), total Beta Human Chorionic Gonadotrophin hormone 2.39mIU/ML (<25 mIU/ML) and Alfa Fetoprotein 0.73 (<7.22). Serum Aldosterone and Cortisol were within normal limit. Her karyotype was 46XY. Total serum testosterone (T) was found elevated for woman/girl that was 275 ng/dl (4-20ng/dl), with 5-alfa dihydrotestosterone (DHT) 257 pg/ml (250-999 pg/dl), T/DHT Ratio 10.7 (8-16), Dehydroepiandrosterone-sulfate (DHEA-S) 169 µg/dl (8.5 to 109 µg/dl), 17 alfa hydroxyprogesterone level 1.44ng/ml (<0.26-1.74 ng/ml) and Androstenedione level 1.29 ng/ml (0.3-3.5 ng/ml). MRI pelvis showed bilateral undescended testes in inguinal canal and well-formed prostate gland & seminal vesicles with uterus and ovaries not visualized (Figure 2). Differential diagnosis of 46, XY DSD due to 5 Alfa reductase deficiency, Congenital Adrenal Insufficiency Syndrome and 17β-Hydroxysteroid Dehydrogenase Deficiency were discussed with our multidisciplinary team. Patient was personally interviewed in presence of multidisciplinary doctors (Endocrinologist, Psychiatrist, Urologist) and the parents. Gender assignment was done as female with informed consent from patient and the parents. She was treated initially with

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Androgen Deprivation Therapy (Leuprolide, Bicalutamide) Estrogen supplementation (/Conjugated Estrogen/Premarin, Estradiol/Valest) and Aldactone (to reduce virilization). After an interval of 3 weeks, bilateral testes removal was done laparoscopically and both testes were found atrophied (Figure 3). She was further planned for genitoplasty and breast implantation (if needed) surgery. She is doing well under follow up.

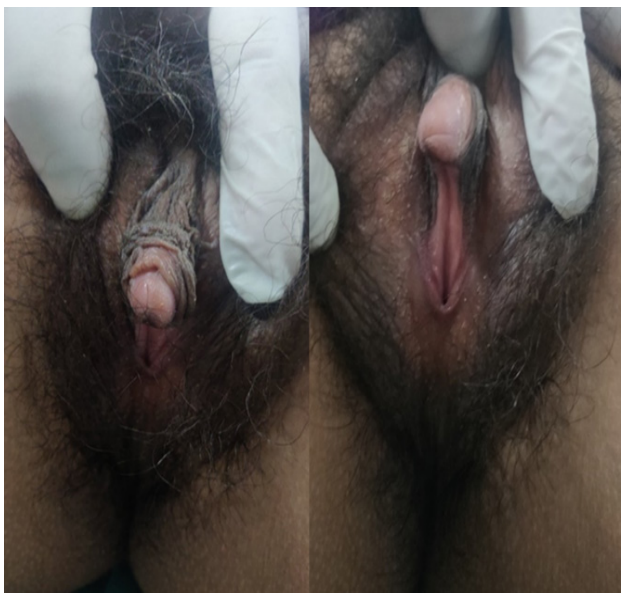

Figure 1: Small Phallus with perineal hypospadias, absent scrotum and male pattern pubic hair

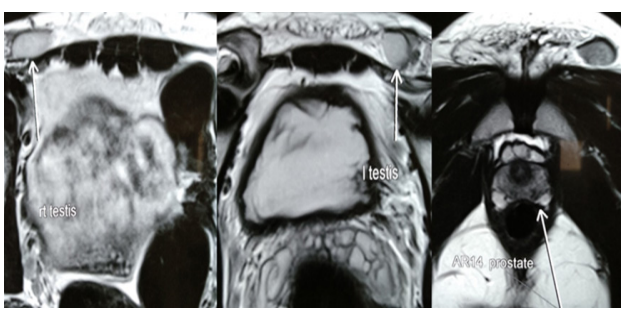

Figure 2: MRI showing bilateral undescended testes in inguinal canal, well developed prostate with no uterus

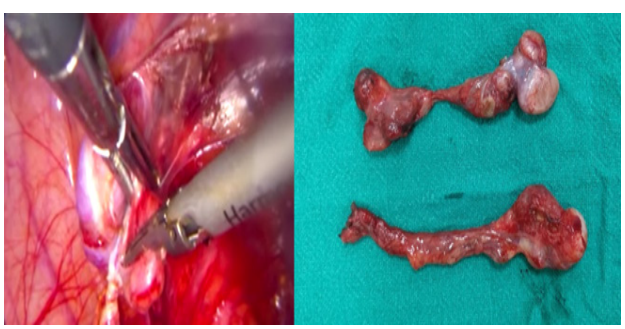

Figure 3: Bilateral atrophied testes removed laparoscopically
DISCUSSION

Genetic males with DSD (i.e., 46, XY DSD) can present with female external genital phenotype, ambiguous, or a micropenis (stretched penile length <2.5 SD for age). It is caused by incomplete intrauterine masculinization with or without the presence of Müllerian structures. It results either from decreased synthesis of testosterone or DHT or from impairment of androgen action (3)
Majority of 46, XY DSD have male gonads but in some of them no gonadal tissue is found. Patient may develop normal female external genitalia due to complete absence of virilization. They generally seek medical attention due to the absence of breast development and/or primary amenorrhea at pubertal age.(1)
Precocious diagnosis of this condition allows a better therapeutic approach, therefore thorough clinical assessment including family and prenatal history, complete physical and genital examination is advised. The diagnostic evaluation of DSD includes Hormonal measurements (LH, FSH, Inhibin B, anti-Mullerian hormone (AMH) and steroids), Ultrasonography imaging, cytogenetic and molecular studies are the diagnostic modalities. Gonadal Biopsy and/or endoscopic/laparoscopic exploration are required in very few cases.(3)(1) Ultrasound easily reveals the presence or absence of Müllerian structures, can locate the gonads and can also identify associated malformations. Therefore, it is considered as the first and often the most valuable imaging modality in DSD.(4) Genitography and cystourethrography can show the type of urethra, the presence of vagina, cervix, and urogenital sinus.
Studies of 46, XY DSD have focused largely on aspects of gender development such as satisfaction with gender of rearing, sexual orientation, gender identity, and gender role (GI/R).
Sometimes it is difficult to reach the diagnosis and identify the actual cause behind the 46, XY DSD. As in our case, we concluded differential diagnosis of 5 Alfa reductase deficiencies, Androgen Insensitivity Syndrome (AIS) and 17β-Hydroxysteroid Dehydrogenase Deficiency. The clinical points in favour of 5 Alfa reductase deficiency are clitoral-like phallus, bifid scrotum, pseudo-vaginal perineo-scrotal hypospadias, penile urethral plate, enlarged prostate and 46, XY karyotyping, whereas, Testosterone & DHT Ratio was 10.7 (<30), which was not in favor. This was not AIS because female distribution of adipose tissue, female breasts and external genital development. 17β-Hydroxysteroid Dehydrogenase Deficiency was excluded due to normal Androstenedione level in spite of enlarged prostate. However Testosterone was low for normal pubertal boy which also could be attributed to atrophied bilateral undescended testes.
DSD may carry a social, cultural and hormonal stigma. These are effect modifiers for gender role. Gender-role change occurs at different rates in different societies. DSD has multiple level relations with fertility, marriage, employment, economic independence, religious views, philosophical views and literacy. (5)
This is a case of delayed diagnosis. Greater opportunity for the patient's involvement and satisfaction in the decision process of gender assignment is the advantage of delayed diagnosis. Negative consequences of development of self-esteem and reduced gender satisfaction within cultures with low incidence of disease are the disadvantages. (6) Self-esteem, social adjustment, financial burden and future planning of the child are the difficulties for the parents. They get worry about risks, benefits and potential complications of treatment and non-treatment options. (2)
Doctors role must be centred at reasonable patient standard. Multidisciplinary team approach (Endocrinologist, Psychiatrist, Urologist) are needed for the thorough discussion and planning of management. Disclosure of diagnosis, prognosis, grave consequences, probable outcomes, expected post-treatment course, risks, benefits of alternative treatments and non-treatment are the responsibilities the treating physicians. Conclusion with a

statement of informed consent must be taken with the concerned. (7)
Angle Learning Vector Quantization (ALVQ) might have helped us to reach the diagnosis of our patient.(8)

CONCLUSION

Ambiguous Genitalia is a diagnostic challenge. Gender Assignment is a multidisciplinary task. Fertility and sexual health are the key concern during DSD assessment.

Conflict of Interest: None

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