"Congruency the ART of Being Real" - 46XY DSD Due to 5 α Reductase Deficiency - Challenges in Decision Making

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Abstract

Disorders of sexual development (DSDs) are heterogenous group of disorders characterized by discrepancy in chromosomal, gonadal, and phenotypic sex. DSD is a Medico-Social Emergency. 5 α reductase type 2 deficiency is one of the rare causes of 46 XY DSD. The degree of under virilization varies from clinically female to a near male phenotype. Müllerian structures were absent. At puberty, there might be features of virilization. Gender incongruence or dysphoria occurs frequently during puberty. An important marker for diagnosis is an elevated testosterone to dihydrotestosterone ratio in the basal state or following HCG stimulation. All 46 XY DSD require an appropriate molecular diagnosis prior to gender assignment and gender reassignment surgery. Gender reassignment surgery and/or Gonadectomy should be performed only after 18 years if there are compelling indications like suspicion of malignancy or presence of gender dysphoria or gender incongruence.

Keywords: 46 XY DSD, 5 α reductase type 2 deficiency, disorders of sexual development, gender dysphoria

Disorders of sexual development [DSDs] are heterogenous group of disorders characterized by discrepancy in chromosomal, gonadal and phenotypic sex.[1] DSD is a Medico-Social Emergency considering the dilemma in gender assignment, management of life-threatening adrenal crisis and timing of gender reconstruction surgery.

Differential diagnoses of 46 XY DSD without adrenal insufficiency are,

a. Gonadal dysgenesis
b. Androgen insensitivity syndrome
c. Androgen biosynthetic defects
   i. Steroid 5 α reductase type 2 deficiency [SRD5A2]
   ii. 17 β Hydroxysteroid dehydrogenase deficiency.

SRD5A2 deficiency is one of the common causes of 46 XY DSD.[1] 5α reductase type 2 enzymes are required to convert testosterone to potent androgen dihydrotestosterone, which is involved in the virilization of external genitalia and the development of prostate and seminal vesicles.

When to Suspect SRD5A2 Deficiency?

The degree of under virilization varies from clinically female to a near male phenotype. The most common clinical phenotype in 46XY DSD due to SRD5A2 is female-like external genitalia with palpable gonads [Figure 1]. In addition, they may present with a bifid scrotum, blind vaginal pouch, clitoris like phallus, hypospadias and testes located in the inguinal canal or in the labio-scrotal folds [Figure 2] at infancy. At puberty, there might be features of virilization along with Gender incongruence or Gender dysphoria.[2]

The classic hormonal profiles of these patients may include age-appropriate normal FSH and LH with normal or elevated testosterone levels contrasting with low dihydrotestosterone levels. An important marker for the diagnosis is an elevated testosterone to dihydrotestosterone ratio in the basal state or following HCG stimulation. T:DHT ratio >30 confer a high specificity (99%) but poor sensitivity (11%), a cutoff value of >10 is associated with moderate specificity (72%) and

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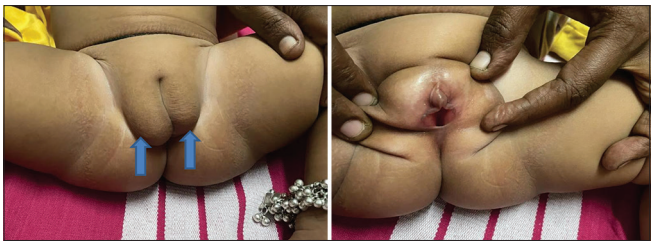

Figure 1: (a) Female like external genitalia with bilateral palpable gonads. (b) Microphallus and proximal hypospadias

sensitivity (78%).[3] Once biochemically confirmed, all cases of 46 XY DSD should undergo molecular genetic analysis to confirm the diagnosis as well as to predict the natural course of 46 XY DSD. In addition, appropriate genetic diagnosis is vital for gender assignment, sex of rearing and genital reconstruction surgeries.

Gender Assignment

There is significant phenotypic as well as biochemical heterogeneity in patients with different homozygous/compound heterozygous pathogenic genotype as well as same genotype.[4] Sex assignment at birth and sex of rearing is challenging in view of complex nature of phenotype and genotype. Most of the infants with SRD5A2 deficiency are reared as females in India according to previously published literature.[5] In addition, more than 70% of SRD5A2 deficiency individuals who are reared as female, had gender dysphoria in adolescence, and most of them wanted gender reassignments as male.[5] In the contrary, SRD5A2 deficient individuals from other countries with female gender assignment at birth preferred female sex at adolescent age.[4]

Gender dysphoria in adolescent manifests as difficulty in wearing school uniform meant for girls, difficulty in using girl's toilet. The reasons for dysphoria [or] pubertal virilization in female-assigned sex of SRD5A2 deficiency is a consequence of enhanced 5 α reductase type 1 and residual 5 α reductase type 2 activity.[5]

Decision Making at Multidisciplinary Level – Need of the Hour

Multidisciplinary committee in Tertiary care Institute involving Neonatologist, Pediatrician, Pediatric surgeon, Psychiatrist, and Endocrinologist should counsel the parents in periodic intervals regarding gender assignment, sex of rearing, pros and cons of gender-changing surgeries in newborn and chances of gender dysphoria in adolescence. Lack of interdisciplinary coordination may be a source of confusion regarding gender assignment and sex of rearing. For example from Pediatric Surgeon point of view especially in 46 XY DSD due to SRD5A2 deficiency with microphallus and hypospadias, it will be easier to make them as female by doing orchiectomy with [or] without feminizing genitoplasty/clitoroplasty or clitoral reduction.

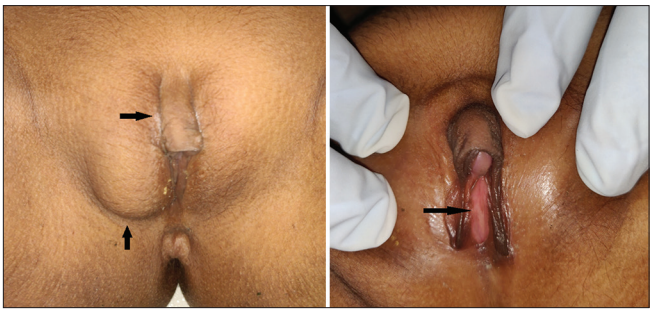

Figure 2: (a) Microphallus and proximal hypospadias with unilateral palpable gonads in labioscrotal area. (b) Ventral urethral groove

Sex Reconstruction Surgery – Legal Issues

Decision on nature and timing of gender reassignment and genital reconstruction surgery should not be done in hurriedness since surgeries like orchiectomy are irreversible. It is indicated only if there is an life-threatening emergencies like urosepsis or suspicious of malignancy. In addition to psychological issues, there are various legal issues for gender-changing procedures. No uniform guidelines are available regarding the timing of sex reconstruction surgeries on individuals with DSD with 5 α reductase type 2 deficiency. Recent guidelines by Government of Tamil Nadu, suggest the formation of Institute multidisciplinary team in all DSD cases and decision on nature and timing of surgery to be made with the family by acknowledging the psychological impact involving in DSD management.[6]

Learning point

- In all 46XY DSD, appropriate biochemical diagnosis, if possible genetic diagnosis should be done before sex assignment [or] sex reversal surgery.
- According to the published research, as well as the natural course of SRD5A2 deficiency, it will be appropriate to assign the sex as a male in concordance with genetic sex.
- Gender changing surgery/gonadectomy should be performed if required only after 18 years with consent of parents and the concerned individual unless there is compelling indications like suspicion of malignancy.

Abbreviations

DSD- Disorders of Sexual Development / Disorders of Sexual Differentiation.

SRD5A2- Steroid 5 α reductase type 2.

T- Testosterone.

DHT- Dihydrotestosterone.

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Conflicts of interest

There are no conflicts of interest.

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