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A Story of A Boy with 5α-Reductase 2 Deficiency Who are Reared As Girl – A Rare Case Report

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Abstract | **Case Report**

5-Alpha reductase deficiency is a rare 46XY disorder of sex differentiation (DSD) caused by mutations in the 5-alpha reductase type 2 gene (SRD5A2) located on chromosome 2p23. This disorder was previously termed as familial incomplete male pseudohermaphroditism, pseudovaginal perineoscrotal hypospadias. Affected patients have a deficiency of the 5-alpha reductase type 2 enzymes, which becomes partially or totally unable to convert testosterone into dihydrotestosterone (DHT) which is being responsible for the development of the external genitalia, prostate, and urethra in the male fetus. Here, we report a case of a 16-year-old girl who presented with primary amenorrhea, ambiguous genitalia, and lack of breast development. USG of W/A & MRI of pelvis show no uterus or ovary like structure, shaft of the penis and testicles are noted in the scrotal sac. All of the serum hormone profiles were normal except for raised serum total testosterone. Testosterone to DHT ratio (T/DHT) was elevated (>20). A chromosomal study revealed a 46XY karyotype. After proper counselling, male gender assignment was planned and reconstructive surgery was performed and hormonal replacement therapy was started. In conclusion, the diagnosis of 5-alpha-reductase 2 deficiency may be suspected in infants with ambiguous genitalia or in adolescents or young adults with the characteristic phenotype and serum hormone profiles.

Keywords: 46XY disorder of sex development (DSD), 5α-reductase, Male pseudohermaphroditism, SRD5A2 gene, DHT.

INTRODUCTION

Dihydrotestosterone (DHT) is essential for the normal development of male external genitalia. DHT is derived from testosterone (T) by a process catalyzed by the membrane-bound steroid 5a-reductase enzyme [1]. Impaired DHT synthesis caused by 5alpha steroid reductase deficiency (5α-reductase deficiency) can lead to incomplete masculinization of the external genitalia in subjects with a 46XY karyotype [1]. The clinical spectrum of a 46XY individual with 5α-reductase deficiency at birth can range from complete female appearance of the external genitalia to nearly complete male phenotype. Most patients, however, present with genital ambiguity and are diagnosed in infancy. At puberty 46XY patients show virilisation without breast development, often accompanied by gender identity change, from female to male in individuals in whom gonads had not been removed [2]. The enzyme steroid 5α-reductase exists as two isoforms, 5α-R type 1 and 5α-R type 2, which have a different expression pattern. Type 1 isoenzyme is encoded by the SRD5A1 gene located on chromosome 5 and expressed at low levels in the prostate, whereas type 2 isoenzyme is encoded by the SRD5A2 gene that maps on chromosome 2 and is expressed at high levels in the prostate and in many other androgen sensitive tissues [3]. Although most individuals with 5α-reductase deficiency are identified in the neonatal period because of ambiguous genitalia, some are misdiagnosed as androgen insensitivity syndrome, as they often present with the same clinical phenotype, while others escape recognition completely.

Case History

A 16 years old patient presented with the complaints of poor development of secondary sexual characteristics and primary amenorrhea. She was born

of a non-consanguineous marriage, at term by vaginal delivery at home without any perinatal complication. There was no H/O maternal virilisation or any drug intake by mother during pregnancy. The child did not have H/O salt crisis or failure to thrive. The developmental milestones and growth were normal and the child had an average scholastic performance. During adolescence, the patient had development of pubic hair but no axillary hair.

On examination, normal body habitus, and axillary hair stage-I and pubic hair stage IV with female pattern. Breast development stage-I. Genitalia examination shows, phallus-4cm, both gonads were palpable into labioscrotal sac, firm in consistency, labioscrotal sac is rugosed & pigmented, perineal urethral opening is present blind vaginal pouch with presence of posterior labial fusion. EMS score is 6.

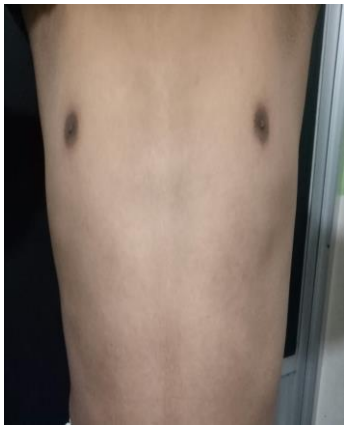

Fig-1: Lack of breast development

Fig-2: Phallus with testicles in the scrotal sac

Fig-3: Pseudovaginal perineoscrotal hypospedias

LABORATORY INVESTIGATION AND RESULTS

Chromosomal analysis showed a normal male 46XY karyotype. On pelvic MRI, ovaries and uterus were absent, shaft of penis is noted, and testicles are noted in the scrotal sac on both sides. The diagnosis of 5α-reductase deficiency was suspected based on biochemical findings & hormonal profile at base line and following hCG stimulation test. As shown in Table 1, the patient's Testosterone to DHT ratio (T/DHT) was elevated before and further increased after hCG stimulation.

Table-1: Results of the hCG stimulation test

Hormone	Before	After
Testosterone ng/ml	5.39	12.61
DHEAS ng/dl	117	139
DHT pg/ml (250-990)	230	278
T/DHT (<12)		>20

Table-2: Hormone analysis

Hormone	Result
FSH (mIU/ml)	6.32
LH (mIU/ml)	9.93
Estrogen (pg/ml)	<10

Table-3: ACTH stimulation test

	0 min	30 min	60 min
ACTH (pg/ml)	33.2		
Basal cortisol (nmol/L)	283	511	710
17OH progesterone(ng/ml)	0.56	0.86	1.12

The diagnosis of SRD5A2 was confirmed by high T/DHT ratio. The subsequent and difficult decision to be made was the possible gender change based on culture and religion, consequent maintenance or removal of the gonads. Patient's gender identity was properly explained to the patient and his parents, his parents. Patient also counselled about his disease, future plan- male gender assignment is indicated. But in this critical age, initially patient didn't accept the fact, as it is very unfortunate for a person who reared as female, suddenly came to know that he is biologically a male person. We have started tab. clomiphene citrate 50mg OD which improve spermatogenesis and serum testosterone level & then plan for injection HCG & Inj. Testosterone and underwent reconstructive surgery for male gender assignment. He was advised to follow up 3 monthly to see change of phallic growth, volume of testicles, S. testosterone level (pooled).

Fig-4: Before

Fig-5: After

DISCUSSION

5α-reductase 2 deficiency is an autosomal recessive form of male pseudohermaphroditism caused by mutations in the SRD5A2 gene. Over 50 different mutations have been described [3]. The typical clinical features in 46XY males with 5-alpha-reductase 2 deficiency are those reported in the two originally recognized families as follows [4, 5]. (1) The external genitalia usually are predominately female at birth, with the exception of clitoromegaly in some, so that most affected males are raised as females. A variable degree of virilization occurs at the time of puberty. (2) The internal urogenital tract is male, consisting of epididymis, vasa deferentia, seminal vesicles, and ejaculatory ducts that empty into a blind-ending vagina. The absence of müllerian duct derivatives indicates that anti-müllerian hormone is produced and acts normally.

A wide spectrum of phenotypes was reported in a subsequent study of 55 patients with 5-alpha-reductase 2 deficiency including the following [6]: clitoromegaly was present in 27 (49 percent), microphallus in 18 (33 percent), and normal female external genitalia in only four (7.3 percent). 40 patients (72 percent) were initially assigned to female gender, and of these, five (12.5 percent) switched to male sex at puberty.

Concentrations of serum testosterone and estrogens are similar to those in normal men. The level of serum luteinizing hormone (LH) is normal in about one-half of subjects and slightly elevated in the rest. Levels of serum follicle-stimulating hormone (FSH) are elevated. Because of the defect in 5-alpha-reductase 2, the ratio of serum testosterone to dihydrotestosterone is increased, basically in adults and after administration of human chorionic gonadotropin (hCG) in childhood. In the initial descriptions, affected subjects were identified because phenotypic females failed to menstruate and developed variable virilization at adolescence. Approximately 55 percent of affected subjects have a blind-ending or pseudovagina in which the Wolffian ducts terminate in the upper vagina. 40 percent of the Wolffian ducts terminate in the perineum on either side of the urethra. The remainder is sufficiently virilized to be assigned male gender at birth. The testes are invariably outside the abdominal cavity either in the inguinal canals, labia majora, or scrotum and spermatogenesis is impaired.

Gender role behavior can change from the female sex of rearing to male at the time of expected puberty. In large extended kindred from the Dominican Republic, as an example, 18 of 19 subjects initially raised as females subsequently changed gender-role behavior to male at the time of puberty [7]. In other reports, approximately 50 to 60 percent of affected individuals assigned female sex in infancy and virilizing in puberty changed their gender role behavior to male. The percentage of patients changing gender role was much lower (12.5 percent) in the report described above[4], perhaps due to different societal responses to the condition in the different communities studied.

The diagnosis of 5-alpha-reductase 2 deficiency may be suspected in infants with ambiguous genitalia or in adolescents or young adults with the characteristic phenotype and serum hormone profiles. Measurement of basal concentrations of serum testosterone and dihydrotestosterone is usually sufficient for diagnosis after the expected age of puberty. The ratio of serum testosterone to

dihydrotestosterone was >20 in affected subjects in the extended kindred from the Dominican Republic and in another nine unrelated Brazilian families [7]. In the latter study, the ratio ranged from 35 to 84 in affected subjects as compared to 8 to 16 in normal subjects. In adults, measurement of the ratio of serum testosterone to dihydrotestosterone after administration of hCG or testosterone does not increase discrimination between affected and normal men. Definitive diagnosis of the mutation in the steroid 5-alpha-reductase 2 enzyme can be made by cDNA analysis using peripheral blood, biopsy material, or fibroblast cultures [8].

Gonadectomy should be performed to prevent or minimize virilization and to prevent development of tumors in inguinal or labial testes. We started tab. Clomiphene citrate 50mg OD which improve spermatogenesis and serum testosterone level and are planning to start Inj. HCG & injection testosterone. Although pharmacologic doses of testosterone esters may raise serum dihydrotestosterone concentrations to the normal range and cause acne and growth of facial and body hair, phallic growth is minimal in adults, and the long-term safety of this treatment is not established. The results are different in prepubertal subjects. He was advised to follow up 3 monthly to see change of phallic growth, volume of testicles, S. testosterone level (pooled). Within this period, he underwent reconstructive surgery for male gender assignment. This patient may be helped to lead a near normal life if periodically supervised for pubertal progress. Appropriate psychological support for the patient and family is also important.

Based on the findings of the present case, it is highly recommended that patients presenting with primary amenorrhea, ambiguous genitalia, and lack of breast development perform serum hormone profiles (LH, FSH, 17-OH Progesterone, DHEAS, and hCG stimulation test and measurement of testosterone to DHT ratio) to reveal this rare disorder.

CONCLUSION

5α-reductase deficiency, although rare, should be suspected in any girl presenting with primary amenorrhea and pubertal virilisation. In patients with 5α-reductase deficiency diagnosed so late, the management is highly problematic and requires extensive psychological evaluation and support of the patient and his family for the final decision of gender assignment as well a later on. To avoid these complications every effort must be made to establish the underlying molecular defect in every newborn with Disorder in Sexual Development.

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