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Sex Assignment and Re-Assignment in Patients with Steroid 5-Alpha Reductase Type Two Deficiency: The Psycho-Social, Religious and Cultural Challenges

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ABSTRACT

Background: Steroid 5-alpha reductase type two deficiency (5 ARD 2) is a rare autosomal recessive disorder of sexual development. The lack of the enzyme, 5 - alpha reductase, that converts testosterone to dihydro testosterone, results in the external genitalia that may be appear atypical, normal to ambiguous external genitalia. Materials and Methods: A retrospective review of patients with 5 - alpha reductase type two deficiency were included. A coordinated multidisciplinary team of specialists were involved. Psych -social, cultural and religious factors were analyzed. Results: Four patients, from three families, among 12 patients, who were diagnosed with 5-alpha reductase type two deficiency in 46 XY disorders of sex development were wrongly assigned female sex at birth due to abnormal external genitalia. Their age ranged between birth to 12 years. Signs of virilization which occurred at 12years of age in one patient led to the diagnosis of the other. The other two patients were diagnosed during the investigation of ambiguous genitalia. The cultural factor was the commonest factor among others, influencing sex reassignment. Level of parental education had no role. Conclusion: Sex assignment remains one of the most clinically challenging and controversial in 46XY disorders of sex development (DSD), in particular that due to steroid 5-alpha reductase type two deficiency. Cultural factors are important, among psychosocial, and religious factors. Given the complexity of the disorder, it is also important to involve a multidisciplinary team of experts in the management.

Keywords: Steroid 5-alpha reductase type two deficiency, Sex assignment, Disorders of Sex Development (DSD), 46XY DSD.

INTRODUCTION

Disorders of male sexual differentiation result from an under masculinized (undervirilized) individual with a 46XY Karyotype and testes (figure 1), due to various causes. It remains a challenging clinical issue in pediatrics endocrinology. (1-8) Steroid 5-alpha reductase type two deficiency is a rare autosomal recessive disorder, initially reported from Dominican Republic and Papua New Guinea. It is also reported outside these ethnic groups. The overall incidence is unknown (9-11). In a community, with increased consanguineous mating, and multiple siblings' involvement, like in Saudi Arabia (12-14), the incidence even may be higher. It results in the lack of generation of dihydroxy testosterone (DHT) from testosterone (T). DHT has a critical role in the external male sexual development, and a shortage of this hormone disrupts the formation of the male external genitalia at birth. Most of patients with steroid 5 alpha - reductase deficiency is assigned female at birth based on their clinical appearance of the external genitalia, however, the general belief such patients should be assigned as male sex.

This is even supported by the available consensus guidelines (15) Psychological, cultural, religious and social factors should be also considered. A coordinated multidisciplinary team of experts should be involved in management. The team consists of pediatric endocrinologist, geneticist, pediatric radiologist, pediatric surgeon, urologist, plastic surgeon, child psychologist or psychiatrist, and another specialist such as a nurse and gynecologist to be consulted whenever needed. (16 -19)

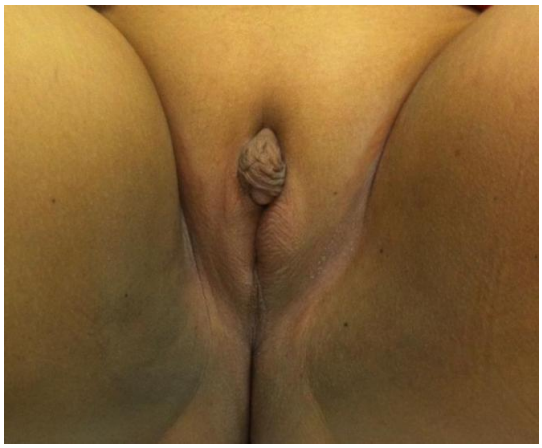

Figure 1: A medical photograph of a newborn infant with normal appearing externalfemale genitalia and clitoromegaly. He had 46 XY karyotype and diagnosed with 5-α- reductase type 2 enzyme deficiency.

In this brief report we describe four patients from three families with the diagnosis of steroid 5 -alpha reductase type two deficiency who were wrongly assigned female sex at birth and discuss the various factors affecting gender assignment at a major referral center, Riyadh, Saudi Arabia.

MATERIALS AND METHODS

This is a retrospective hospital-based study, conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. KKUH is the main teaching institute of the King Saud University and considered as one of the main referral centers in the region. It provides primary, secondary and tertiary health care services for the local population and receives patient's referral from all over the country.

The medical records of patients with 46 XY DSD, diagnosed with steroid 5 alpha reductase deficiency were reviewed for the clinical characteristics and managements, in the period from January 1989 to June 2017 All patients were diagnosed hormonally by utilizing Human Chorionic Gonadotrophin (HCG) stimulated dihydrotestosterone (DHT) / testosterone (T) ratio. (20 - 22) Patients were managed by an expert multidisciplinary team. Psycho-social, religious and cultural impacts were analyzed.

RESULTS

During the period under review, four patients with 46XY DSD, from three families were wrongly assigned a female sex due to severe undervirilization. Their age ranged from birth to 12 years, with variable clinical characteristics, Table 1. All patients presented with variable degrees of ambiguous genitalia. No female internal organs were illustered, with testis present at variable

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positions of the inguinal canal. Signs of virilization which occurred at puberty, 12years, led to the diagnosis in a sibling, while the other two were diagnosed at birth. The dominance of male sex in the community and, hence; male preference of male facilitates sex reassignment. The level of education of parents has no major role. Despite of repeated surgeries and the effects of puberty patients still suffering from small (microphallus) genitalia. They feel shy and frustrated, and had an aggressive behavior. This is a unique challenge which need a lifelong medical care and health education with psychosocial support.

Table 1: Clinical characteristics of patients with 46XY disorders of sex development (DSD), due to Steroid 5 alpha reductase enzyme 2 deficiency

Patients	Family	Sex assigned at presentation/Age	Clinical features	Sex of rearing (Sex re-assigned)/Age	Family history of DSD
1	1	Female/Birth	Ambiguous genitalia, Micropenis withchordee and bilateral undescended testicles	Male/4 days	-ve
2	2	Female/4 years	Urogenital sinus with bifid, emptyscrotum	Male/4years	-ve
3	3	Female/12 years	Normal appearing female genitalia with marked clitoromegaly, and pubic hair of T3.	Male/12 years	+ve
4	3	Female/8 years	Normal appearing female genitalia	Male/8years	+ve

NB: -ve; negative, +ve; positive, T; Tanner stage.

DISCUSSION

The five alpha reductase enzyme type two deficiency (5aR2D) is a rare autosomal recessive 46 XY disorder of sex development (DSD) that results in the reduced ability to produce dihydrotestosterone (DHT) from testosterone (T), a hormone that is required for the development of the external genitalia. Initially recognized in large families in the Dominican Republic and Papua New Guinea and later reported from other countries world-wide, with several gene mutations. The high frequency represents the effect of consanguineous mating. The estimated incidence is approximately one in 5500 live births. (1-3, 5, 11, 20, 23-30).

Sex of a newborn is typically assigned at birth on the basis of genital appearance of the external genitalia However, this need to be revised (reassigned) in certain conditions of sexual development disorders, such as, steroid 5 alpha reductase enzyme 2 deficiency, where the external genitalia could be atypical. It has variable psychological and social consequences, which require special support. Unfortunately, in spite of the availability of the consensus statements on the subject and the long clinical experience it remains a controversial issue and a challenge to the practicing medical care providers and parents. (1-4, 9, 30-42) Most of the patients with this disorder are assigned female sex at birth based on the appearance of the external genitalia, however, a male sex should be assigned at birth or reassigned later. Furthermore, virilization that occur at puberty, a hallmark feature of the disorder, will occur. (43- 47) as illustrated in our patients. Many of those individuals will have the potential to be fertile (48-50) and the possibility of fatherhood. These are the main indicators for male sex assignment.

The management is so complex and challenging. The combination of medical and Surgical options of therapy are essential for a better outcome. This will start with utilizing dihydrotestosterone creams (3,21,51). Early surgical intervention is vital. A multidisciplinary team of experts in the field (16-19) should be involved. This also, requires parental and, when appropriate, patient education. This should be frank and open. Families must be given enough time to digest and understand the information. Lifelong support and education should continue. The penis could be reconstructed by various phalloplasty procedures (52-55).

CONCLUSION

Sex assignment remains one of the most clinically challenging and controversial in 46XY disorders of sex development (DSD), in particular that due to steroid 5-alpha reductase type two deficiency. Cultural factors are important, among psychosocial, and religious factors. Given the complexity of the disorder, it is also important to involve a multidisciplinary team of experts in the management.

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Conflicts of Interest

The author has no conflict of interest to declare.

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