CASE SERIES

DISORDERS OF SEX DIFFERENTIATION: EVALUATION AND MANAGEMENT, A DILEMMA

Sadaqat Jabeen, Mahnaz Faisal, Maleeha Nisar

Department of Gynaecology, MTI lady Reading Hospital, Peshawar-Pakistan

The term intersex used in the past has been replaced by "Disorders of Sex Differentiation". In this condition the development of chromosomal, gonadal or anatomical sex is atypical. This problem creates anxiety to the parents and a challenge for attending doctor. The problems faced by the individual are sexual, reproductive, sex of raring, placement in the society and psychological impact. The optimal management of the patient should be individualized by multidisciplinary team. Three cases of Disorders of Sex Differentiation (DSD) are presented with different causes and presentations. Two cases carrying XY karyotype pattern, while one case was of XX. The diagnosis of swyers syndrome, 5 alpha reductase deficiency and congenital adrenal hyperplasia was made on the basis of genital tract development, hormonal analysis and karyotyping. The strange feature which was common in all these cases was the wish of patients as well as family members to adopt sex of raring as male.

Keywords: Disorder of sexual development; Intersex gonadal dysgenesis; Awyers syndrome; Congenital adrenal hyperplasia; 5 alpha reductase deficiency

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INTRODUCTION

Disorders of Sex Differentiation (DSD) is congenital disorder, where development of chromosomal, gonadal or anatomical sex is atypical.[1] in the past the term intersex was used but Chicogo consensus in 2005 replaced the nomenclature by DSD.[2,3] The overall incidence of DSD is 1 in 5500.[4,5] The new classification has taken three main diagnostic categories, 46XY DSD (Female male), 46XX DSD (female female) and true hermaphrodites.[6,7] The evaluation and management are complex and multidisciplinary team approach is needed. Besides sexuality and fertility main problem is the sex of raring and psychological impact on the child. Health professional should emphasize to the families that child with DSD has the potential to become well-adjusted functional members of society. Here we present three cases of different presentation, with different karyotyping pattern but all adopted sex of raring as male.

CASE -1

A 10 years old boy was referred from paediatric surgical unit with the complaints of ambiguous genitalia and passage of urine through a hole in the perineum since birth. In his past surgical history, he had circumcision at 2 year of age, orchidopexy and herniotomy at the age of 4 year. Plastic surgery of genitalia at the age of 8 year alone with cystourethroscopy by paediatric surgeon and urologist. Phenotypically he was male, his height was 4 feet and weight was 31 kg. On genital examination phallus was <2 cm, no penile urethra, urethral orifice was at the base of the phallus and vaginal orifice was below the urethral orifice. Labia majora was of pre pubertal form, there was a swelling about 2×2 cm, mobile and firm in consistency in the right labia majora. On pelvic ultrasound uterus was small about 2.5×1cm, ovaries or testes could not be seen. His testosterone, FSH and LH levels were normal male like. His karyotyping was 46XY. Biopsy from the right sided swelling showed early testicular tissue.

On the basis of all these findings he was diagnosed as a case of mixed gonadal dysgenesis (Swyer syndrome). Diagnosis was declared to him as well as parents and management options were discussed. They decided the sex of rearing as male. Total abdominal hysterectomy was performed as well as testicular swelling was removed. He was referred to plastic surgeon for reconstruction of external genitalia. Vaginal obliteration was done by plastic surgeon. His physical appearance was also modified as male.

CASE-2

A 16 years old girl was brought to gynae OPD with primary amenorrhea. She was accompanied by her sister who was having same problem. On clinical examination she was female looking. Her height was 5 feet and weight was 55 kg. Breasts were not developed and axillary and pubic hair was sparse, tanner stage $B_0P_1A_1$. On examination of external genitalia, there were sparse pubic hair and phallus was <2.5 cm. There was hypospadias at the base of the phallus, scrotum was splited into two palpable masses in the lower part. Vagina was blind showing only a dimple. On ultrasound uterus, fallopian tubes and ovaries were absent. There was testicular tissue in both scrotal swellings. Her hormonal profile FSH, LH and testosterone was within the male range and DHT was decreased. Her karyotype was 46XY. Diagnosis of 5 alpha reductase deficiency was made. Diagnosis was declared to the parents as well as to the patient, they chose her sex of raring as male. She was referred to the plastic

surgeon for urethral and phallus reconstruction and removal of the testes. Her physical appearance was also converted to male like (see picture case No 2). Endocrinologist was consulted, she was put on testosterone and was advised for regular follow-up.

CASE-3

A healthy 22 years old male presented with ambiguous genitalia and pain hypogastrium that was of sudden onset 6–8 months back. He was born of consanguineous marriage. His family history was significant, his paternal cousin was having the same signs and symptoms. On general physical examination his height was 153 cm, weight was 87 kg. His breast were not developed and his axillary and pubic hair were having male pattern. His external genitalia was ambiguous, having scrotal sac with no testis and a small penis (phallus 3.5 cm). His abdomino-pelvic scan showed a uterus measuring about 38×18×22 mm, anteverted with normal contour and texture and collapsed cavity. Both ovaries were normal looking. High resolution B scan of scrotum showed both testicles were absent. On laboratory investigations his LH was 11.92 miu/ml (normal 1.0–12.5), FSH 4.58miu/ml (normal 1.0–12.1), Serum Testosterone 7.44ng/ml (normal 2.5–12.5), Prolcatin was 205.37 uIU/ml (normal 42.5–414). Other investigations showed high levels of 17 hydroxy progesterone and low levels of plasma cortisol levels. His karyotype was 46XX. This young male was diagnosed as having Adult Type congenital Adrenal Hyperplasia. Management was started by multidisciplinary approach involving Gynaecologist, Endocrinologist and a Psychiatrist. He and his family wanted total abdominal hysterectomy for rearing male sex due to social and economic reasons. He was counselled about changing gender and further treatment but refused strongly to change his physical appearance. He has been started on steroid therapy for few months as advised by endocrinologist and has been asked for follow-up, so we can proceed with his management accordingly.

Figure-1 (Case-1): Swyer syndrome: External genitalia showing enlarged clitoris and hypospidias

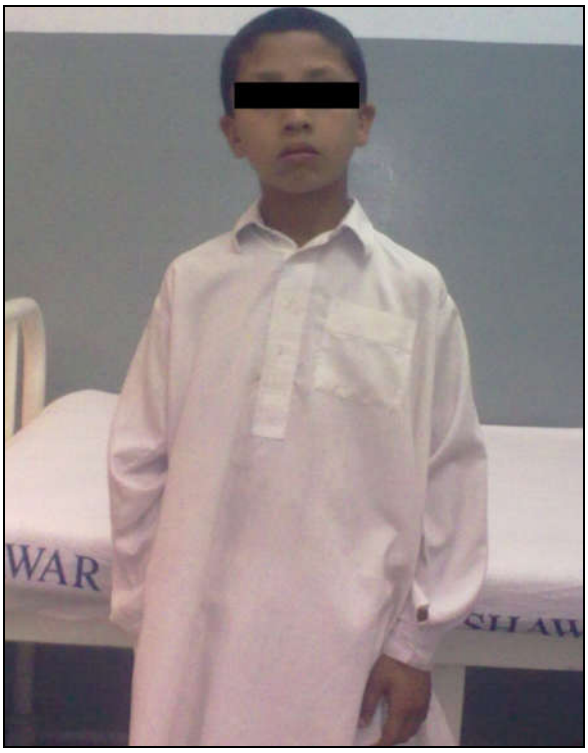

Figure-2 (Case-1): Physical appearance adopted as male

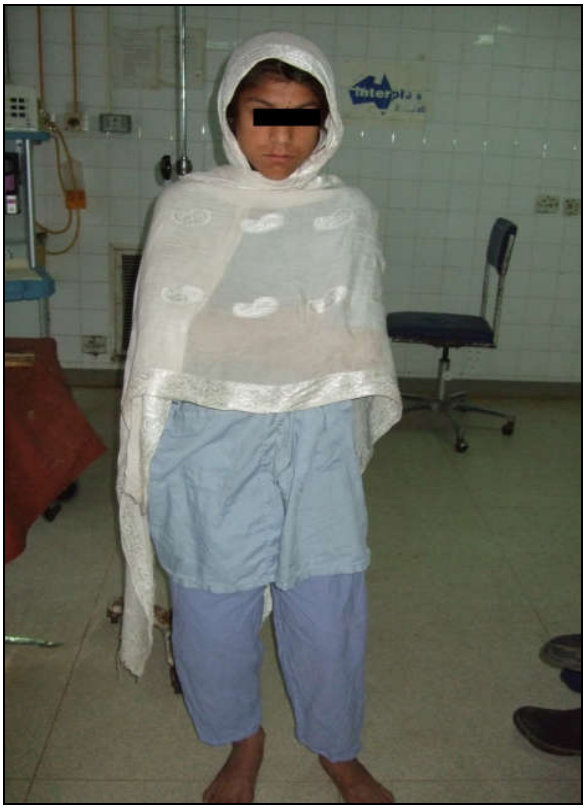

Figure-3: (Case-2) Case of AIS, Female appearance before treatment

Figure-4 (Case-2): After treatment

Figure-5 (Case-3): Adult CAH (46XX)

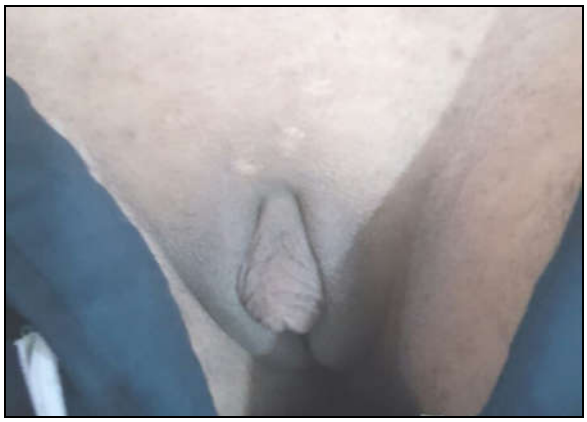

Figure-6 (Case-3): Adult CAH showing enlarged clitoris

DISCUSSION

Confirmation of a baby sex at birth is common curiosity, but when the sex assignment at birth becomes difficult due to mixed feature of external genitalia it causes severe anxiety to parents and challenging dilemma for health provider. Patient may present with phenotypically female while she will be carrying XY chromosomes or vice versa. We have presented three cases belonging to all the categories of DSD. Their common feature was the wish to adopt male as sex of rearing.

First case was of swyer syndrome where SRY gene on Y chromosome is absent, which results in inhibition of suppression of anti-mullerian hormone.[8] This results in the development of female genital tract in male from mullerian ducts. The incidence is 1:100,000 live born males.[9] This exactly appeared in the 1st case where the patient was female phenotype with 46XY chromosomes and there was development of uterus, tubes and vagina and under developed testes. We don't have the facility of testing SRY gene so it was not done. It is easy to rare such patients as female and there is possibility of development of breasts and functioned uterus by administration of hormone replacement therapy as describe by Azidah A his case report.[10]

In our case the patient and family strongly opted to be a male due to social reasons. So, hysterectomy, salpingectomy and gonadectomy was performed as the reminant gonads may result in seminoma formation. Similar cases have been described by Patna Yak RI[11] and Bagec G[12]. The diagnosis of swyer syndrome may be challenging, sometimes the mullerian duct derived structures i.e. uterus and fallopian tube may be hidden or not well developed and analysis of genetic mutation may not be available or helpful.

The second case was Androgen Insensitivity Syndrome (AIS). It is the X linked recessive condition with the quoted incidence of 1 per 20400 live born males.[13] There are two types complete AIS and partial AIS depending upon the amount of residual receptor.[14] Both have 46 XY karyotypes. In complete AIS patient has female external genitalia, clitoris and vaginal introitis.[12,15] The phenotype of partial AIS may range from mildly virilised female external genitalia with clitoromegaly or mild under virilised male external genitalia. Our case seems to have partial AIS as he had 46 XY, non-developed breast and pubic hair, slight clitoromegaly, hypospadias and scrotal swelling containing gonad. Treatment depends upon the type of AIS and also patients / relatives desire for sex of raring. Treatment is hormone replacement therapy and orchidectomy to prevent the possibility of malignancy.[16] Patient with partial AIS may be treated with testosterone and/or dehydro-testosterone or therapy may vary depending on the nature of gene defect.[17] As in our case patient opted sex of raring as male so orchidectomy was performed and he was put on testosterone by endocrinologist.

There is sometimes diagnostic dilemma in differentiating between swyer syndrome and AIS.[18] In both conditions the karyotypes are 46 XY but absence of breast and presence of uterus and pubic hair makes the possibility of swyer syndrome.

The 3rd case was of non-classical late onset adult congenital adrenal hyperplasia. It involves a group of autosomal recessive disorders, which result from deficiency of enzyme 21 hydroxylase or 11 beta hydroxylase involved in the synthesis of cortisol, aldosterone or both. Males and females are equally affected and the average incidence is 1:15000 live births.[19] Diagnosis is based upon hormonal levels of 17-Hydroxyprogesterone, Testosterone, DHEA Sulphate, Andostenadion, cortisol and plasma rennin.[20,21] In our patient beside phenotypical characteristics, karyotype was 46XX, genital organs were female like and the level of testosterone and 17-hydroxyprogesterone were increased.

The treatment is based up the principle of replacing normal glucocorticoids and psychological support. Reconstructive surgery of genital tract may help patient acquiring sexual and fertility problems. This patient was counselled for sex of raring as female as there are good chances of acquiring menses, sexuality and fertility by medical as well as surgical treatment. He was put on steroids by endocrinologist. He strictly refused to adopt female status due to social reasons as he was the earning person for his family. He also insisted for removal of uterus and tubes he was referred to psychiatric colleague and counselling and follow up was advised.

CONCLUSION

Early diagnosis of females presenting with amenorrhea is important. Treatment of these problems need multidisciplinary approach. These patient needs care of puberty, sexuality, fertility, psychological support and adjustment in the society.

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Address for Correspondence:
Sadaqat Jabeen, Professor HOD gynae A unit, MTI lady Reading Hospital, Peshawar-Pakistan
Email: drsadaqatjabeen@gmail.com