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Case Report

A case report: 46 XY-disorder of sexual development

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ABSTRACT

Authors report a case of a 6-year-old child with syndromic 46, XY disorder of sexual development. From the birth patient was assigned female. Physical examination showed dysmorphic features and ambiguous external genitalia. Cytogenetic analysis of cultured peripheral blood lymphocytes revealed a male karyotype. The result of the chromosomal investigation showing male genetic sex, together with the ambivalent aspect of the external genitalia and gonads that are exclusively testes led to the diagnosis of 46, XY disorder of sexual development. The clinical management will help the child and the family deal effectively with this condition A multidisciplinary approach to this problem involving pediatricians, specialists in the field of endocrinology, genetics, surgery and psychiatry is necessary in order to reach a prompt and correct diagnosis and treatment.

Keywords: 46 XY disorder of sexual development, Ambiguous external genitalia, Sex reassignment

INTRODUCTION

Intersexuality is the condition of a person whose sex chromosomes, internal and external genitalia and/or secondary sex characteristics are neither exclusively male nor female. In these conditions chromosomal sex is inconsistent with phenotypic sex. It is estimated that about 1% of live births exhibit some degree of sexual ambiguity and between 0.1% and 0.2% of live births are subjects of specialist medical attention, including surgery.[1] Understanding of the causes of sexual ambiguity has evolved from the establishment of the hormonal etiologies to defining the genetic basis of these disorders. Intersexuality has a complex etiology, being the result of different mutations of specific genes involved in the process of sexual differentiation, which leads to different molecular events.[2]

The advances in identifying the molecular basis of abnormal sex and the ethical issues related to management of these conditions led to a review of their nomenclature and classification. The term "disorders of sexual development" (DSD) is proposed instead of intersex, referring to congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. A new classification of DSD includes three major groups: sex chromosome DSD, 46, XX DSD (disorders of ovarian development, androgen excess and others) 46, XY DSD (disorders of testicular development, disorders in androgen synthesis or action and others). According to the revised nomenclature, instead of male pseudohermaphrodite, under virilisation of an XY male and under masculinisation of an XY male the term "46, XY DSD" is proposed.[3,4] Male pseudohermaphroditism is characterized by the presence of 46, XY karyotype, exclusively male gonads and ambiguous or female external and/or internal genitalia, caused by incomplete virilization during prenatal life. Male pseudohermaphroditism encompasses a group of disorders that can arise from a variety of conditions, including dysgenesis of the gonads during embryological development, abnormalities of gonadotropins, inborn errors of testosterone biosynthesis and many abnormalities of androgen target cells.

CASE REPORT

A 6-year-old patient reared as a female presented with ambiguous genitalia since birth at Obstetrics and Gynaecology department of civil hospital, Ahmedabad on June,2017. Patient was born at full term by vaginal delivery. There was no any history of non-consanguineous marriage.

There was no history of maternal virilization during pregnancy or prenatal exposure to androgenic drugs. Family history also was not significant. Since birth patient was raised as a girl child till age of 6 years but likes to play outdoor games and dress like boys and having abnormal genital features.

On general examination

Patient' height-118 cm, weight-16 kg with no abnormality detected in general examination. Cardiovascular system, respiratory system were normal. Abdomen was soft with no palpable mass.

On examination of secondary sexual characters

Not developed.

On examination of external genitalia

- Phallus (2.5X1 CM)with redundant preputial skin present.
- Single perineal opening(hypospadiasis)
- Bifid scrotum
- Right testes in scrotum, left testes palpable
- Single anal opening.

Investigations

- HB-9.9 gm/dL
- WBC-10,800/cumm
- Platelets-4,40,000/cumm
- S. Androstenedione(19/9/2017)-<0.30ng/mL
- S. Dihydrotestosterone(19/9/2017)-62.10pg/mL
- S. FSH-1.41 mIU/mL
- S. Testosterone-2.1 ng/mL(19/9/2017)
- Chromosomal karyotyping :Congenitally normal (46-XY) chromosomal complements

USG Abdomen-pelvis

- Approx. 14x6 mm sized testis like structure in right superficial inguinal region.
- Approx 13x5 mm sized testis like structure in left superficial inguinal region.
- Uterus and B/L ovaries absent.

After all investigation's patient was referred to pediatric surgery department.

Management

- In view of managing such complicated scenario multidisciplinary approach was required. Patient was referred to paediatric surgery and psychiatric department.
- Patient's cystogenitoscopy was done on June, 2017in which following findings were summarised:
- Normal bladder, B/L ureteric opening normal, bladder neck normal, pseudo vagina(1.5 cm common channel, blind ending pouch present, no E/O cervix.

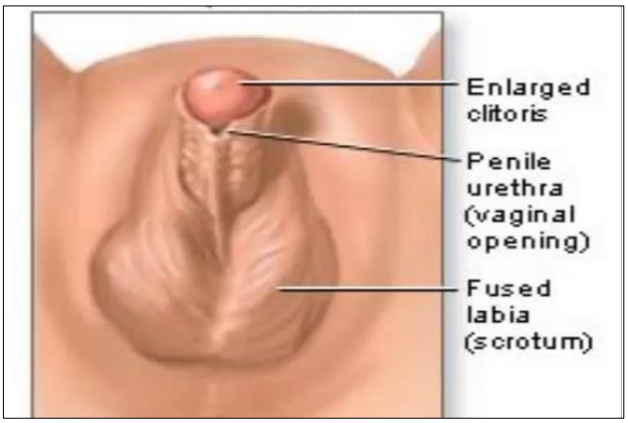

Figure 1: External genitalia in sexual developmental disorder.[5]

Along with it left Orchiopexy was done.

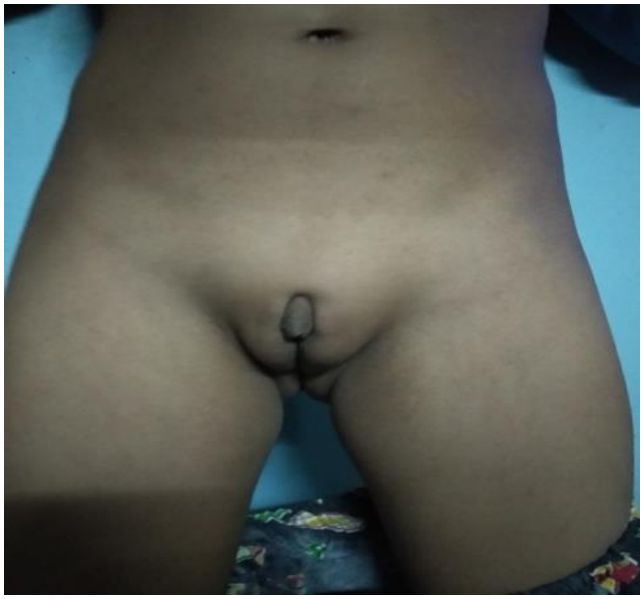

Figure 2: External genital appearance before operation (June 2017).

On further plan of management Testosterone stimulation test was applied. Hormonal levels {Testosterone, LH/FSH,DHT, AMH} were monitored After that Inj HCG 1500u SC/IM given daily for 3 days. On day-4 S.

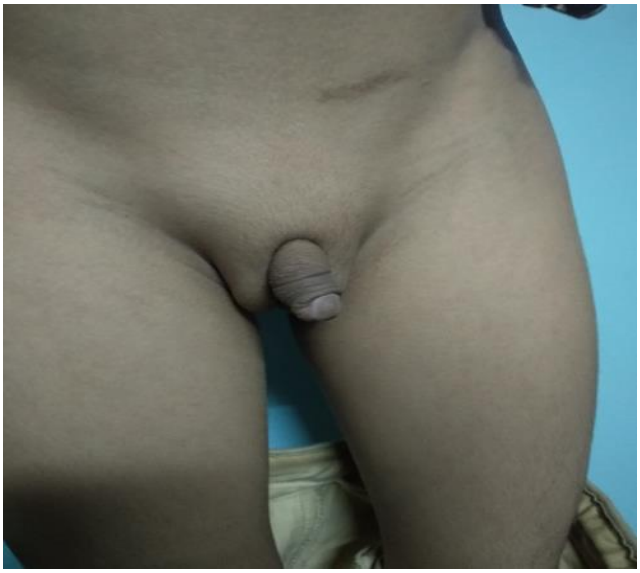

Figure 3: External genital appearance after operation (November 2018).

Testosterone and S. DHT levels were measured. It was observed that patient was responsive to Testosterone stimulation test. Now surgical management was planned in which on Feb,2018 byar's flap was transferred to repair midshaft and more proximal hypospadiasis of penis. On October,2018 tube urethroplasty was done and penis was totally reconstructed. After it patient was given 2 doses of testosterone to maintain physiological level of male androgenic hormones and lastly patient was called on Nov 2018 for U-calibration.

DISCUSSION

The term 'Disorders of Sex Development' (DSD) is now proposed to define congenital conditions in which a dysharmony between chromosomal, gonadal and anatomical sex exists.[3] Genital ambiguity occurs in 1 in 4500 births.[6] Many conditions can lead to the appearance of ambiguous genitalia in a newborn. Male pseudohermaphroditism is defined as the incomplete masculinization of the external genitalia in patients with a normal, 46,XY karyotype. Affected individuals have gonads that are testes, but their genital ducts, external genitalia or both are not completely masculinized.[7] This type of pseudohermaphroditism can result from decreased synthesis of testosterone as a consequence of dysgenetic testes, associated with mutations in factors related to testicular development.[8,9] Other causes are represented by defects in androgen formation attributed to enzymatic defects along the conversion of cholesterol to testosterone, which occur due to autosomal recessive mutations. These affect enzymes involved in the side chain cleavage reaction (due to impairment of the steroid acute regulatory protein of 20, 22 desmolase), or 3β-hydroxysteroid dehydrogenase (3β-HSD), 17α-hydroxylase/17-20 lyase, and 17β-hydroxysteroid dehydrogenase.[10] High levels of DHEAs suggest a 3β-HSD deficiency. Undervirilization in these cases occurs because synthesis of testosterone is impaired in both adrenals and testes. DHEA, even elevated, is a weak androgen. Management issues are those of an undervirilized male with normal sensitivity to testosterone. The diagnosis is usually confirmed by the distinctive pattern of adrenal steroids: elevated 17hydroxypregnenolone, DHEA and renin. Impaired secretion of Anti Müllerian hormone, failure of target tissue response to testosterone and dihydrotestosterone or Anti Müllerian hormone and failure of conversion of testosterone to dihydrotestosterone may also lead to male pseudohermaphroditism.[11,12]

Male sexual differentiation depends on the secretion of testosterone by fetal Leydig cells. This is initially under the influence of placental hCG, during the critical period of male sexual differentiation and, then, fetal pituitary LH. Male pseudohermaphroditism, sexual infantilism and adrenal insufficiency are consequences of very early defects in the synthesis of all steroids affecting the conversion of cholesterol to pregnenolone. Enzymatic defects in testosterone biosynthesis are very rare. Defects in the androgen action are the most common causes. These include mutations in the androgen receptor gene and mutations in the steroid 5α-reductase 2 (5α-RD2 gene), which encodes an enzyme that converts testosterone to dihydrotestosterone in the male urogenital tract. Androgen receptor disorder, also called androgen insensitivity syndrome, is divided into two forms: the complete form and the partial form. In the complete form the patient has normal female external genitalia. Patients with the partial form present early with ambiguous genitalia, usually in the form of clitoromegaly with severe hypospadias. In both conditions, there is absence of female internal reproductive organs, which can be verified by ultrasound or laparoscopy. Androgen insensitivity syndrome occurs because of an abnormality in the androgen receptor, thus plasma testosterone levels are normal and when subjected to human chorionic gonadotropin stimulation test, there is a normal response, revealing that Leydig cells are functionally normal. The androgen insensitivity syndrome is caused by a mutation of the androgen receptor gene.[13] Patients with defects in androgen action have a deficiency of 5α–reductase, which is encoded by the SRD5A2 gene. Testosterone cannot be converted to the more active dihydrotestosterone at the external genitalia target cells. These patients secrete normal testosterone and müllerian inhibitory factor and so they have normal internal male genitalia, but they present early with severe hypospadias. The classical syndrome is characterized by a predominantly female phenotype at birth and significant virtilization without gynecomastia at puberty.[14] The aspect of the external genitalia in these patients depends on the cause, and ranges from mild hypospadias with some clitoral hypertrophy to complete phenotypic females.[15] In the evaluation of any child with ambiguous genitalia, it is essential to determine the karyotype. A male karyotype (46,XY) in the presence of incomplete masculinization and bilateral testes establishes the diagnosis of male

pseudohermaphroditism. Although on rare occasions male pseudohermaphroditism may result from gonadal dysgenesis, these patients in addition have müllerian structures due to the lack of a müllerian inhibitory factor. In patients with gonadal dysgenesis, there is no or low testosterone level and no accumulation of testosterone precursors, while in patients with enzymatic defects, there is low testosterone level and accumulation of plasma precursors, depending on the site of block. This, however, is not the case if the defect is in 20, 22desmolase, the first step in the pathway from cholesterol to testosterone, where no rise in testosterone or testosterone precursors will be produced. These patients have bilateral testes, which differentiates them from cases of gonadal dysgenesis.[16] A new born infant born with ambiguous external genitalia presents a major diagnostic challenge and a social and medical emergency. Disorders of sexual development with ambiguous genitalia require prompt investigations and early gender assignment. Once the diagnosis of genital ambiguity is made, on-going psychological support for the patient, parents, and other family members is critical. Evaluation should be made efficiently to ensure that the appropriate gender is assigned, potential life-threatening complications are recognized, necessary medical, surgical and psychological interventions begin promptly. The complexity of the problem requires a multidisciplinary team working together. Affected patients and their parents should be provided with full information to make an appropriate choice for gender assignment. The aims of management in a newborn with DSD should be the provision properly planned surgical procedures with psychological support to the family, potential sexual function and fertility.

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