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Original Research Article

The Pattern of 46XX Disorders of Sex Development (DSD) in a Major Referral Hospital, Riyadh, Saudi Arabia

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ABSTRACT

Background: Disorders of sex development (DSD), formerly known as ambiguous genitalia, is common in this part of the world, and so challenging. In this study, we reviewed the clinical pattern of a cohort of patients with 46XX DSD in a major referral centre over 25 years in Riyadh, Saudi Arabia.
Design and Setting: A retrospective, hospital-based study was conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia during the period January 1989 and December 2014.
Methods: Medical records of children with the diagnosis of 46XX DSD were retrospectively reviewed. Data included age, sex at presentation and of rearing, results of the relevant laboratory and radiological investigations, family history, drug intake, as well as, signs and symptoms of diseases in the mother.
Results: During the period under review, a total of 63 patients with 46XX DSD were evaluated. Congenital adrenal hyperplasia (CAH) was the commonest (96.8%) aetiology and only two patients had isolated clitoromegaly. The patient's age ranged between newborns to 13 years of age. Seven patients needed sex re-assignment.
Conclusion: Congenital adrenal hyperplasia was the commonest aetiology seen in 96.8% of patients. In Saudi Arabia, where consanguineous mating is high with multiple siblings' involvement within the family this was not unusual.

Keywords: ambiguous genitalia, pattern, 46XX DSD, Saudi Arabia.

INTRODUCTION

Disorders of sexual development (DSD), formerly known as intersex conditions or ambiguous genitalia are among the most fascinating conditions encountered by the clinician. It represents a true medical and social emergency. DSDs vary in frequency, depending on their etiology. This might be either virilized females 46XX DSD, figure 1, or under-virilized males 46XY DSD. DSD requires a medical attention, with an experienced multi-disciplinary team to reach a definite diagnosis. A 46XX karyotype indicates that the child is a genetic female who was exposed to excessive amount of androgens during fetal life, either due the most common congenital adrenal hyperplasia (CAH) or rarely, maternal androgen production or ingestion. On occasion

translocation of pseudo-autosomal part of the Y chromosome along with a mutated SRY gene to an X chromosome occurs. The result is partial masculinization of the genitalia in a 46XX newborn. [1-4]

This article is an attempt to define the clinical pattern of a cohort of patients with 46XX DSD in a referral hospital, Riyadh, Saudi Arabia over 25 years.

MATERIALS AND METHODS

The study population consisted of all patients presented or born at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia over 25 year-period (1989-2014). King Khalid University Hospital is the main teaching hospital of King Saud University and considered as one of the major referral hospitals in the central province (Riyadh), Saudi Arabia. The hospital provides primary, secondary and tertiary health care services for the local population and also receives patients referred from all over the country.

Medical records of patients were reviewed and included; age at presentation, sex at presentation and of rearing, clinical presentation, family history, drug intake, symptoms and signs of disorders in the mother, the appropriate diagnostic (radiological and serological) tests and karyotype. Routine tests included; follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol adrenal androgens and electrolytes.

RESULTS

Table: Aetiology of ambiguous genitalia in 63 patients

Diagnosis	No. of patient	%
▪ Congenital adrenal hyperplasia	61	96.8%
○ 21-α-hydroxylase deficiency	51 (48 SW)	-
○ 11-β-hydroxylase deficiency	9	-
○ 3-β-hydroxysteroid dehydrogenase deficiency	1 (1 SW)	-
▪ Isolated clitoromegally	2	3.2%
Total	**63**	**100%**

Salt-wasting - SW

During the period under review; a total of 63 patients were seen with 46XX DSD, due to variable aetiology (Table). Congenital adrenal hyperplasia was the commonest (96.8%), with multiple siblings involvement within the family. No maternal illness nor drug intake was noted. Only two patients had isolated clitoral enlargement, figure 2. Their age ranged between newborns to 13 years of age. Seven patients needed sex re-assignment, which was denied by parents in four, due to psychosocial reasons. This was, later, accepted by two.

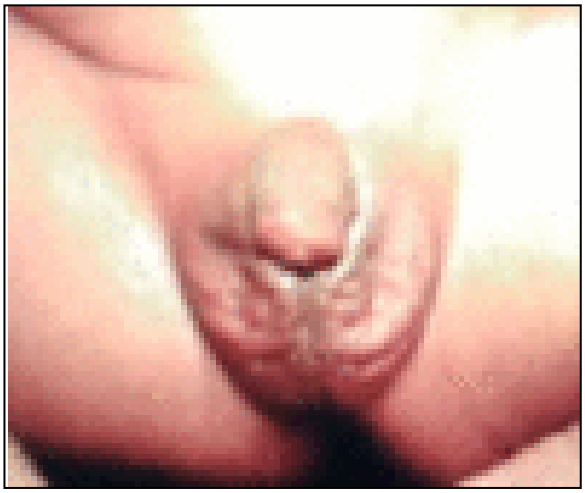

Figure 1: Ambiguous genitalia is a 46XX patient diagnosed with congenital adrenal hyperplasia due to 21-α-hydroxylase deficiency. Note, the severe masculinization with normal looking hyperpigmented male genitalia but with no palpable gonads.

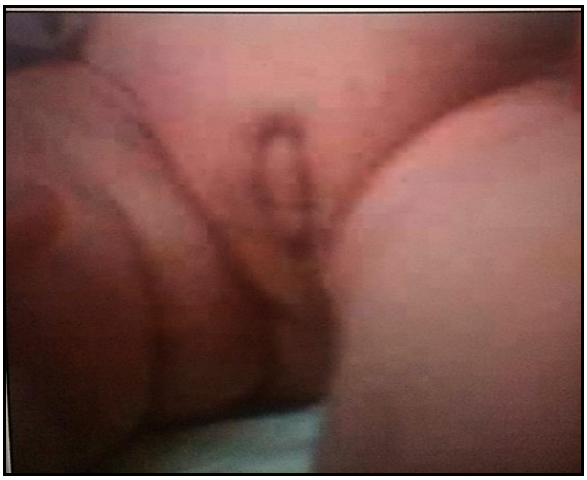

Figure 2: A newborn baby girl with (46XX DSD), she had clitoral enlargement.

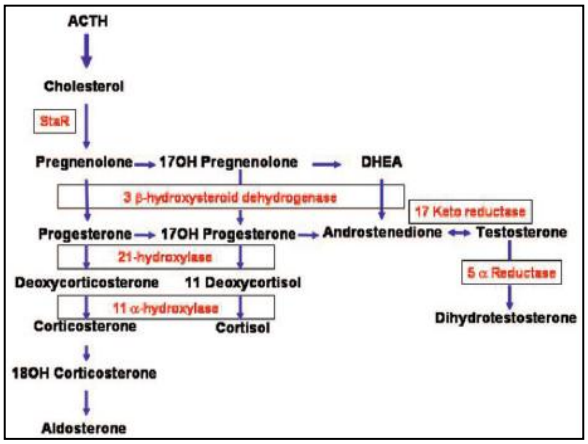

Figure 3: Adrenal and gonadal steroidogenesis pathway.

DISCUSSION

The newborn whose genitalia are ambiguous presents a diagnostic challenge to the physician and emotional crisis for the family. Evaluation and diagnosis must proceed rapidly to determine the sex of rearing and to initiate necessary medical interventions. An experienced multi-disciplinary team constitutes of pediatric endocrinologist, geneticist, pediatric surgeon or urologist and psychologist should provide the care. [3-9]

Virilized female neonates exhibit a wide-range of external genital appearances, from mild clitoromegally, to complete labioscrotal fusion and urogenital sinus, which can open onto the perineum or on the shaft of clitoris / phallus. [3]

The most common cause is a form of congenital adrenal hyperplasia, where the deficiency of the enzyme 21-α-hydroxylase, as in our series. This leads to increased androgen production, figure 3, and therefore, virilization associated salt-wasting can hint into the diagnosis. Less common enzyme deficiencies are of 11-β-hydroxylase which could results in hypertension without salt-loss, and 3-β-hydroxysteroid dehydrogenase deficiency. [3,6-10]

The isolated clitomegaly reported in two of our patients. Placental aromatase deficiency is a rare autosomal recessive disorder leading to an elevated androgen concentration in the female fetus. Aromatase hormonally converts-testosterone to estradiol and androstenedione to estome, limiting the concentration of androgen in the fetus. This is which we cannot prove. Other uncommon causes of virilization which we ruled out include maternal adrenal or ovarian tumor and material exposure to progestational agents or synthetic androgens during pregnancy. [3] This is in contrast to Al Mulhim and Kamal [11] where they found in their series, a higher percentage of generalized and local developmental malformation.

Severely virilized patients may initially be assigned as male sex, as in this series, and once such assignment has been made, it may be difficult to reverse. Among (46XX) congenital adrenal hyperplasia patient, seven were raised wrongly as males, two refused sex re-assignment. [9-12]

A multi-disciplinary team consisting of a pediatric endocrinologist, pediatric surgeon or urologist, geneticist, and a psychologist should collaborate in ranging such patients. [4-12]

The issue should be discussed clearly with parents and should be raised as females as they could have a high fertility rate. [13]

CONCLUSION

Congenital adrenal hyperplasia was the commonest aetiology, seen in 96.8% of patients. In Saudi Arabia, with a high consanguinity rate and multiple siblings involvement within the family, this was not unusual.

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