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RESEARCH ARTICLE

Disorders of sex Development (DSD); Beyond hormonal aetiology.

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ABSTRACT

Disorders of Sex Development (DSD), are a group of conditions where the biological sex, being male or female, of a baby does not match the genital appearance. Congenital genital abnormalities, isolated or in association with syndromes, can often be confusing and have complex pathology. Here in we report our experience with patients, who presented with various congenital genital abnormalities, referred to our center as DSD. The aim is to highlight the importance of considering this in the differential diagnosis of DSD. During the period under review, 204 patients were referred for the pediatric Endocrine clinic, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, for evaluation of possible DSD. Their age ranged between newborn to 8 years of age. More than sixty eight percent (139 patients) were genetically females (46XX), while 29.4 percent (60 patients) had a male genetic sex (46XY). The majority of patients with female genetic sex (46XX) had congenital adrenal hyperplasia (CAH), while androgen resistance (AIS) was the commonest in male genetic sex (46XY). Of interest, to observe an increase in the percentage of patients with congenital genital anomalies of 14.8 percent (31 patients), with no hormonal aetiology in association with DSD. Further, specific genetic studies utilizing the current available technologies. We conclude that clinicians should consider such fact in their management of DSD.

Keywords: Anomaly, Congenital, Disorders of Sex Development (DSD), genetic, hormone, Saudi Arabia.

Introduction:

Disorders of Sex Development (DSD), are a group of conditions where the biological sex (being male or female) of a baby does not match the genital appearance. (Figures 1 and 2)

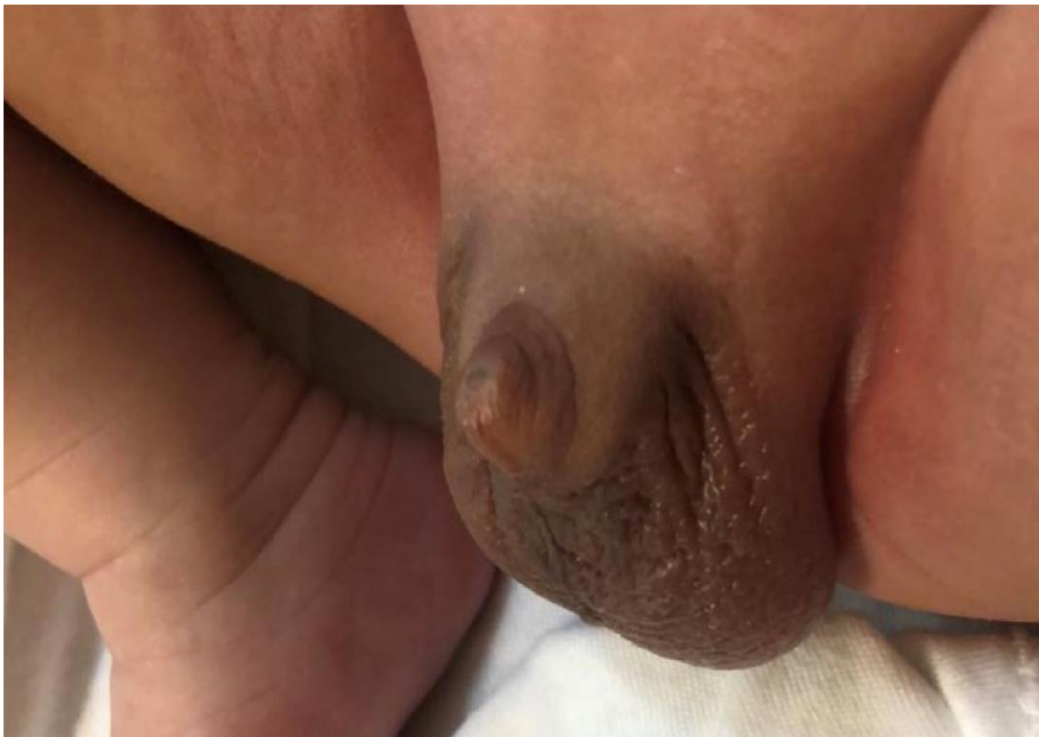

Figure 1
A patient who was assigned a male sex. He was found to have a 46XX karyotype and diagnosed to have 11-b-hydroxydase deficiency. Congenital adrenal hyperplasia.

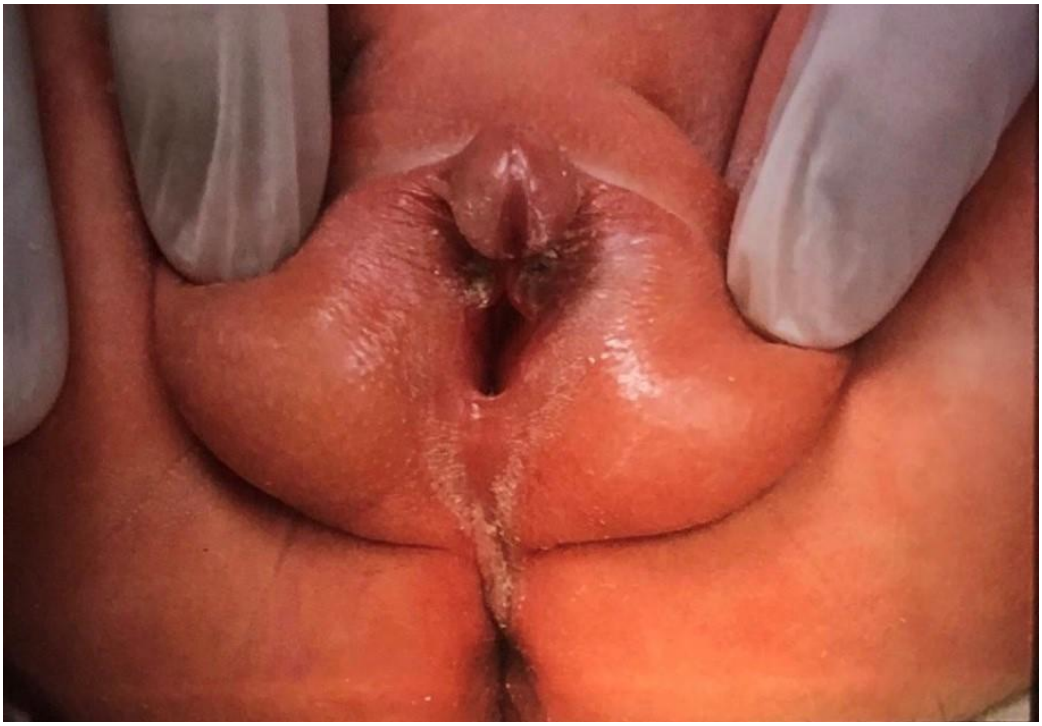

Figure 2
Ambiguous genitalia in a 46 XY DSD with the diagnosis of androgen insensitivity (testicular feminization) syndrome. Note the two palpable gonads (testes) within the labioscrotal folds and urogenital slit.

As a group, they are often challenging to the patients, their families, and health care providers. Patients with DSD are often diagnosed in the neonatal period because of atypical external genitalia. Most patients with DSD are caused by hormonal changes, like congenital adrenal hyperplasia (CAH) or androgen insensitivity syndromes (AIS), while others are caused by chromosomal variations as in Turner syndrome and Klinefelter

syndrome or specific gene mutations that alter development, rather than hormone production or resistance. Structural malformations (like cloacal exstrophy) that occur during fetal development are also known as major causes. These could be a direct effect of exposure to medications or radiation during pregnancy [1-5].

This article primarily aims to highlight and express the importance of including the various causes of DSD. There is no substitute to careful history and appropriate physical examination in order to guide the diagnosis and avoid unnecessary investigations.

Materials and methods:

This is a retrospective, hospital - based clinical study conducted at the Pediatric Endocrine Clinic, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia over more than 30 years. The hospital is one of the main referral hospitals in the capital Riyadh, which receives approximately 5500 delieves per year, and accepts referrals from other parts of the country, Saudi Arabia.

The diagnosis of disorders of sex development (DSD) was based on clinical, radiological, and laboratory findings as recommended by the protocol (3). The appropriate diagnostic (radiological and serological) investigation were done for all patients, Gene studies, laparoscopy or laparotomy were performed when appropriate.

The aetiological diagnosis, the detailed physical examination, and results of investigation were tabulated in a special form before analysis.

Results:

During the period under review a total of 204 patients were evaluated for SDS. Their age ranged from newborn to 8 years of age. One hundred and seventy eight (87.3 percent) patients were caused by various hormonal imbalances, while the other 26 (12.7 percent) patients were associated with variable syndromatic and non-syndromatic malformations (table 1). One hundred and thirty nine (68. 1 percent) patients were genetic females (46XX), while sixty (29.4 percent) patients were having male genetic sex (46 XY), (Table 2). The majority of patients had hormonal imbalances, such as, Congenital Adrenal Hyperplasia (CAH), and androgen disorders, however; various other congenital anomalies were diagnosed within the series. Two cases were diagnosed to have Klinefelter 's syndrome, two with multiple congenital malformations in reminiscent of hydrolethalus and pseudotrisomy 13 syndromes, and two with mosiac Turner's syndrome, while, mixed gonadal dysgenesis, Swyer' s syndrome, and Prader-Willi Syndrome, in one patient each, (Tables 1 and 2).

Of interest, to have one child with extreme prematurity (gestational age of 24 weeks), who had unclear genitalia. Karyotype study revealed 46 XY, with gonads within the inguinal canals.

Table 1, Aetioloical causes of 204 patients with disorders of sex development (DSD)

	No. of patients (%)
Genetic Female sex (46XX)	
-Adrenal defects -Syndromatic and non syndromatic	137 (67.2%) 4 (2%)
Genetic male sex (46XY)	
-Various androgen disorders	38 (18.6%)
-Adrenal defects - Syndromatic and non syndromatic	3 (1.5%) 22 (10.8%)

Table 2: The genetic sex of 204 patients with disorders of sex development (DSD)

Genetic Sex	***Numbers (Percentage)***	***Remarks***
46XX	139 (68.1%)	Two had:- -Mosaic Turner syndrome
46XY	60 (29.4%)	Three had:- -Klinefelter syndrome (2) - Mixed gonadal dysgenesis (1)
Total	199 (97.5%)	*5* (2.5%)

Discussion:

Disorders of sex development (DSD) [1-5] constitute a challenging disorder, which is not that rare worldwide [6,7]. It is comprised of a group of congenital conditions where the biological sex, being male or female, of a baby does not match the genital appearance. While many involve hormone imbalances, like congenital adrenal hyperplasia (CAH), and androgen resistance, however; many studies indicate that a significant number of cases are instead due to, development or genetic factors. In a high consanguineous population, [8] like Saudi Arabia , the majority of patients with DSD had congenital adrenal hyperplasia (CAH)and , variable patients were diagnosed with isolated or multiple syndrmatic and non -syndromatic congenital anomalies [9-14]. High altitude could be another contributing [15,16].

In general, associated anomalies in disorders of sex development, include cardiac (22-23%), renal (16 %), skeletal defects (12%), along with central nervous system . Urogenital sinus and cloacal anomalies are rare . Congenital anomalies are caused by problems during

the fetal development before birth. Several factors contribute to the development of birth defects. Genetic factors, as well as, environment and nutritional. Genetic mutatios play a major role in the occurrence of congenital anomalies. These mutatios may be inherited from one or both parents or occur spontaneously during early development. Further, specific genetic studies utilizing the current available technologies are needed [17-22]. There is scarce information on the exact epidemiology and the frequency of anomalies that may be association with DSD. The majority of those cases have been associated with 46XY DSD. This is in accordance with our observation [23].

There are several literature reports of mosiac Turner's sydrome patients associated with abnormal genitalia, secondary to the presence of SRY gene. Al Mulhim and Kamal [24] reported Similar findings, from Eastern Saudi Arabia.

The field of neonatal care is evolving rapidly, thus a marked improvement in the survival rates and long term health [25]. one of the patients was extremely premature with the recent and rapid advancement in technology, neonatal care improved a great deal, and therefore we will see more pre mature, babies possibly with incomplete development of genitalia.

Conclusion:

Disorders of sex development are caused by variety of causes, with congenital adrenal hyperplasia being the commonest endocrine disorder. However, isolated, and other multiple congenital anomalies that fit into certain syndromes were not rare encounters. A detailed history and comprehensive physical examination can aid the diagnosis, and help avoiding unnecessary investigations.

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Conflict of interest

The authors have no conflicts of interest to declare.

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