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"Should the child be raised as male or female?" The evaluation and management of different causes of ambiguous genital appearance in children

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ABSTRACT

Diagnosing, managing and assigning gender for different causes of ambiguous genitalia in children can be challenging. This article will discuss about the types, diagnosis and treatment of disorders of sex development including congenital adrenal hyperplasia, 46 XY mixed gonadal dysgenesis and 46XY ovotesticular disorder of sex development. This article reports about 3 cases of disorders of sex development. The first case is about a three-year-old girl who was diagnosed with congenital adrenal hyperplasia, genital examination revealed clitoromegaly and a single urogenital sinus; she was managed medically and surgically. The second case is about a one-month-old child with 46XY karyotype, genital examination revealed penoscrotal hypospadias with right palpable and left impalpable gonads. The patient underwent diagnostic laparoscopy in which both female and male internal organs were found; based on these results a diagnosis of 46XY ovotesticular disorder of sex development was made. The third case is about a 3-month-old child with 46XY karyotype, genital examination revealed hypospadias with bilateral impalpable gonads. Diagnostic laparoscopy showed a uterus with a bilateral ovary-looking gonad; histopathology of the bilateral ovary-looking gonads was consistent with testicular tissue. Based on the above, a diagnosis of 46XY mixed gonadal dysgenesis was made. Disorders of sex development are classified into three main categories based on the karyotype, XX, XY and sex chromosome other than XX and XY. Laboratory investigations, karyotype, genetic analysis, imaging, surgery and tissue biopsy, all aid in diagnosing, deciding gender identity and managing different types of disorders of sex development.

Keywords: Ambiguous genitalia, disorders of sex development, ovotesticular disorder, mixed gonadal dysgenesis

Disorders of sex development (DSD) is a broad term that is defined as a congenital discrepancy between the phenotypic and genotypic sex. Disorders of sex development with genital abnormalities sufficient to prompt evaluation occur in approximately 1 in 1000 to 4500 live births [1-3]. The causes of DSD can be classified into 3 categories, DSD in individuals with an XX karyotype, XY karyotype, and sex chromosome complement other than XX or XY. Disorders of sex development in individuals with XX karyotype

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are caused by high levels of androgens either from the adrenal cortex, gonads, or exogenous source; and therefore, lead to virilization in XX infants. Adrenal overproduction of androgens is caused by either congenital adrenal hyperplasia (CAH) or glucocorticoid resistance. Gonadal overproduction of androgens is caused by either XX testicular/ovotesticular DSD or aromatase deficiency. Other causes of XX chromosome DSD include gestational hyperandrogenism. Disorders of sex development in individuals with XY karyotype are caused by low levels of dihydrotestosterone action either due to gonadal dysgenesis or abnormal androgen synthesis or response (androgen insensitivity). Sex chromosome DSD occurs in sex chromosomes other than XX or XY and examples of this subtype of DSD include mosaicism and chimerism.

This article focuses only on DSD that present with atypical genital appearance discordant with the chromosomal sex (also referred as ambiguous genitalia) and it will cover the causes, diagnosis, and treatment of DSD. The aim of presenting the cases is to overview the different types of DSD in general, to review case scenarios of rare types of DSD including 46 XY ovotesticular DSD and 46 XY mixed gonadal dysgenesis, and to discuss the approach of diagnosing and treating such cases.

We selected the cases who initially presented to the endocrine clinic of our tertiary hospital and then they were referred to us, the pediatric surgery outpatient department, and were managed by the same pediatric surgery consultant. We will discuss all the cases in detail below

CASE PRESENTATION

CASE 1

A three-year-old girl was referred to our pediatric surgery department on 1/2020 from another tertiary hospital that doesn't have pediatric surgery service when the child was 13 days of age as a case of neonatally diagnosed congenital adrenal hyperplasia (21-hydroxylase deficiency) with atypical genital appearance. The mother was healthy, no history of consanguinity, and had another child with congenital adrenal hyperplasia. The patient was born full-term by spontaneous vaginal delivery.

Genital examination revealed a clitoromegaly of 3 cm in length, scrotalized labia, no palpable gonads and a single urogenital sinus (Fig. 1); other systemic examination unremarkable.

Investigations revealed a karyotype of 46XX, laboratory tests showed a cortisol of 179 nmol/L, normal range (NR) 4.4-25 nmol/L, Testosterone of 52 nmol/L (NR 0.1-2.4 nmol/L), ACTH of 601 ng/L at birth and 92 ng/L before treatment (NR 7.2-63.3 ng/L), 17 Hydroxyprogesterone of 600 nmol/L at birth and 265 nmol/L before treatment (NR 0.2-5 nmol/L), Androstenedione of 34.5 nmol/L before treatment (NR 2.6-10.7 nmol/L). Improvement of the above values were noted after the initiation of medical treatment with hydrocortisone and fludrocortisone; Testosterone of 5.22 nmol/L, ACTH of 1.2 ng/L, 17 Hydroxyprogesterone of 0.3 nmol/L, and Androstenedione of 0.35 nmol/L after treatment.

The pelvic ultrasound showed a normally appearing uterus and bilateral ovary with no testis. Genitogram was done and showed two linear tracts filling up a bear shape structure likely representing the vagina and the urinary bladder, the common channel measuring approximately 1.5 cm.

At the age of 3 years, the child underwent clitoral reduction and vaginoplasty with the finding of clitoromegaly of 3.5 cm. After inserting a Foley catheter in both, the vagina and the urethra, a flap was created below the vaginal orifice followed by a vertical mid-

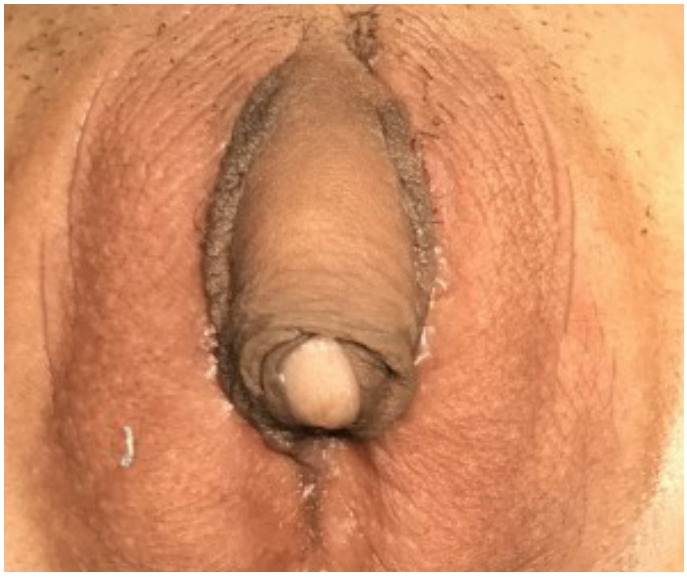

Fig. 1. Clitoromegaly (this picture does not represent the real patient).

line mucocutaneous incision which was made between the vaginal orifice and the flap. Clitoris was fully degloved till the crural separation. The dorsal neurovascular bundle was preserved and parts of the glans and the erectile tissue were excised to reduce their size. The ventral clitoral mucosal tissue was used to create a vestibule and the degloved clitoral skin was used to reconstruct the labia minora. The lateral labio-scrotal skin was used to reconstruct the labia majora. Finally, the flap was sutured along with labia minora and labia majora bilaterally.

CASE 2

A seven-year-old boy was referred to our pediatric surgery department on 1/2016 from a local hospital when the child was one month old due to atypical genital appearance. The boy was born at full-term by spontaneous vaginal delivery. The mother mentioned a history of gestational diabetes which was controlled with diet. There was no prenatal androgens exposure or history of maternal virilization during pregnancy. Also, there was no maternal family history of women who have been unable to conceive or had amenorrhea. The other two siblings of the patient were both normal.

A focused genital examination revealed a peno-scrotal hypospadias with severe penile chordee, right testis was palpable in the scrotum with moderate hydrocele, and left testis was impalpable with hypoplastic bifid scrotum (Fig. 2). Other systemic examination unremarkable.

The laboratory investigations done at one month of age were as follows: chromosomal analysis showed 46XY normal male karyotype, FISH for SRY gene showed the presence of Y chromosome in 100% of the analyzed metaphases, normal 17-OHP and electrolytes, and other hormonal studies were done before and after CGH injection at one year of age and the results were as follows: Testosterone, Androstenedione and Dihydrotestosterone were 0.06 nmol/L (NR 0.1-2.4), 0.53 nmol/L (NR 2-9.3), 0.66 nmol/L (<0.17) before CGH Injection respectively; and 7.23 nmol/L, 0.35 nmol/L, 1.13 nmol/L after CGH Injection respectively. Anti-Mullerian hormone level was 153.5 pmol/L (NR 53-1735). Abdominal ultrasound was done and showed: (The right testis in the right medial inguinal area with hydrocele and the left testis was not clearly seen. Both kidneys appeared normal. A stripe of increased echogenicity seen posterior to the bladder likely represents vaginal tissue. A normal uterus was not seen.). The above information most likely fits the condition of ovotesticular DSD.

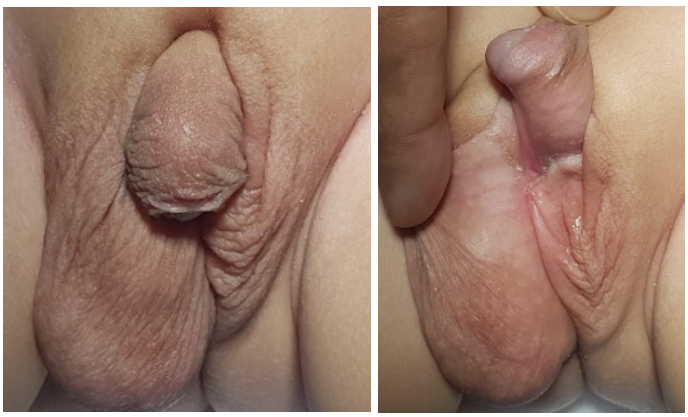

Fig. 2. Genital asymmetry (this picture does not represent the real patient).

At 2 years of age, the patient underwent a laparoscopic left gonadal biopsy, right patent processus vaginalis ligation and right gonadal biopsy; with the following intraoperative findings: on the left side there was a round ligament seen crossing the internal inguinal ring, small atrophic hemi-uterus with fallopian tube and ovary-looking structure was seen, no left testis found. On the right side there were testicular vessels seen crossing the canal passing through the internal inguinal ring, no gonads and no vas deferens were seen. On right inguinal exploration, there was a hernial sac with testis of average size and testicular vessels, but no vas deferens was seen, and small epididymis was seen separated from the testis.

The histopathology report was as follows: the ovarian biopsy was consistent with left ovarian tissue and the testicular biopsy was consistent with right testicular tissue. There was no evidence of gonadoblastoma or other germ cell tumor from both samples.

At six years of age, the patient underwent cystourethroscopy, laparoscopic removal of female internal organs on the left side, and laparoscopic left inguinal herniotomy. The intraoperative findings were atrophic ovarian tissue, atrophic hemi-uterus with soft tissue that looked like atrophic vaginal tissue, and a fallopian tube on the left side. Cystourethroscopic findings were normal urethra with no evidence of urethral fistula. Histopathology of the sample was consistent with atrophic vaginal tissue.

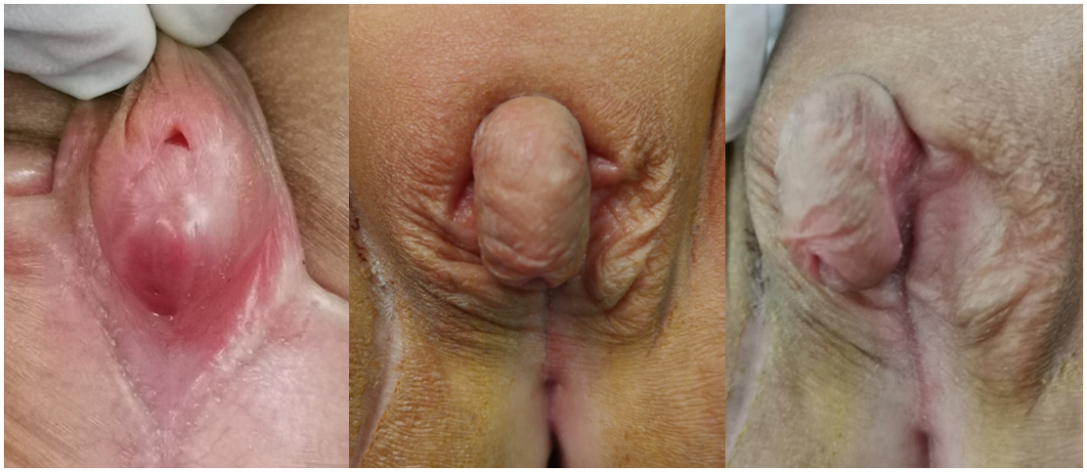

Fig. 3. Coronal hypospadias and hypoplastic scrotum.

CASE 3

A 2-month-old full-term baby was referred to our pediatric surgery outpatient department on 11/2022 from a local hospital due to ambiguous genitalia. The mother was healthy, not on any medications, and no history of maternal virilization. The parents were not consanguineous and no family history of similar condition.

On examination, the child phenotypically looked like a virilized female. Genital examination revealed a phallus of 2.2 cm in length, coronal hypospadias, no vaginal opening, no testicles felt, poorly developed scrotum, and the anus was normal in position (Fig. 3).

Investigations done were as follows: chromosomal analysis of 72 hours of peripheral blood lymphocyte cultures revealed 46XY karyotype with the presence of SRY gene in the Y chromosome. Pelvic ultrasound showed a normal size uterus, normal size bilateral ovaries, no testicles were seen. Laboratory findings were as follows: 17 OH progesterone of 36.5 nmol/L (NR 0.2-5 nmol/L), Androstenedione of 0.47 nmol/L (NR 2-9.3 nmol/L), DHEA-S of 2.82 nmol/L (NR 0.2-4.8 nmol/L), DHT of 0.67 nmol/L (NR < 0.17 nmol/L), Testosterone of 8.35 nmol/L (NR 0.24-0.7 nmol/L). Based on the above findings and information, a diagnosis of partial gonadal dysgenesis was made.

The child underwent diagnostic laparoscopy and cysto-genitoscopy. The cysto-genitoscopy findings were as follows: a 2 cm phallus with mid-penile hypospadias, no verumontanum; at the turn of the urethra, the normal vaginal orifice was seen. The urethra was anterior to the vaginal orifice. Laparoscopic findings were as follows: the uterus seen more well-developed on the right side compared to the left side, both round ligaments were well-formed and entering the in-

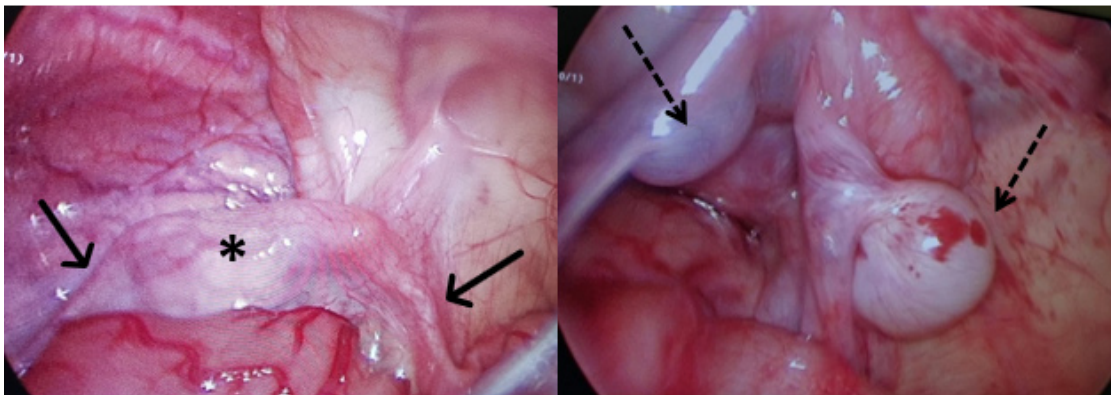

Fig. 4. A) uterus (*) with right and left fallopian tubes (straight line arrow). B) right and left ovaries (dotted arrow)

ternal inguinal ring, both ovaries were normal in size, both fallopian tubes had no fimbriae, two small cysts seen at the junction of the left fallopian tube and the left ovary, no vas deference or testes seen (Fig. 4). Histopathology of the bilateral ovary-looking gonads was consistent with testicular tissue, no ovarian tissue was identified.

DISCUSSION

Disorders of sex development (DSD) should be considered in any infant with frankly atypical genital appearance, in male infants with bilateral nonpalpable gonads, severe hypospadias, or any hypospadias accompanied by unilateral or bilateral cryptorchidism or micropenis; and in female infants with posterior labial fusion, clitoromegaly, urogenital sinus, or gonads palpable in labioscrotal folds or inguinal region.

Initial evaluation of any suspected DSD should include taking a pregnancy and a family history, physical examination, pelvic and abdominal ultrasound, laboratory testing including CAH panel (17-hydroxyprogesterone, 17-hydroxypregnenolone, cortisol, and 11-deoxycortisol), baseline electrolytes, karyotype or fluorescence in situ hybridization (FISH) for SRY, X and Y chromosome probes, and laboratory tests for gonadal function (FSH, LH, testosterone, dihydrotestosterone and AMH).

After the initial evaluation, one would be able to categorize DSD into either XX DSD, XY DSD or mosaicism/chimerism. A subsequent evaluation is then performed to confirm or identify specific causes within a general category of DSD. This includes other steroid precursors to identify rare forms of CAH, ACTH stimulation test (e.g. in XX infants with borderline elevations in 17-OHP), hCG stimulation test, genetic testing and second-line imaging (like retrograde urethrogenitogram). Human chorionic gonadotropin (hCG) stimulation test helps in distinguishing between disorders of abnormal androgen synthesis and abnormal androgen sensitivity; a ratio of testosterone: dihydrotestosterone after hCG stimulation > 10:1 suggests 5-alpha-reductase 2 deficiency [4] and a ratio of testosterone: androstenedione after hCG stimulation < 0.8 suggests 17-beta-HSD3 deficiency [5]. Genetic testing includes AR gene for androgen insensitivity and SRY and NR5A1 genes for testicular/ovotesticular DSD and XY gonadal dysgenesis. Multigene sequencing is becoming increasingly available and cost-effective.

In the first case scenario, history wise there was a positive family history as expected. The clinical examination revealed a clitoromegaly (in XX neonates, clitoral lengths of more than 9 mm are unusual [6-8] and is caused by inappropriate androgen action), a urogenital sinus (one common opening located in the introitus below the clitoris, with internal connection between the vagina and urethra indicating partial but incomplete androgen action) and in some other patients, a posterior labial fusion can also be seen (anogenital ratio > 0.5, which is the distance between the anus and posterior fourchette divided by the distance between the anus and the base of the clitoris/phallus).

The condition was diagnosed neonatally by elevated 17-hydroxyprogesterone. Electrolytes measurement is important for early identification and treatment of salt wasting which is suggested by the findings of hyponatremia, hyperkalemia, hypoglycemia and non-gap metabolic acidosis. Adrenocorticotropic hormone (ACTH) at time of presentation was elevated suggesting primary adrenocortical insufficiency due to CAH. Androstenedione was also elevated. The detection of uterus in XX infants with CAH by pelvic ultrasound is due to the absence of high amounts of AMH produced by Sertoli cells of the testis.

21-hydroxylase deficiency accounts for approximately 95 percent of CAH and it is the most common cause of atypical genital appearance. Other types of CAH include 11-B-hydroxylase deficiency and 3-B-HSD type2 deficiency. Approximately 90 percent of 46XX CAH with Prader II to IV virilization (figure 5) have female gender identity as adults and psychosocial outcomes are generally positive [9]. Surgical treatment for those individuals includes separation of the urinary tract and vagina, labioplasty and clitoroplasty. The separation of the vagina from the common urogenital sinus allows the common urogenital channel to function as the urethra. The separated vagina is then brought out as a separate opening below the urethra (vaginoplasty). This is followed by reconstruction of the labia minora and labia majora next to the opening of the reconstructed vagina. Finally, reduction of the size of the clitoris (for patients with Prader IV or V) using the newer ventral approach technique to pre-

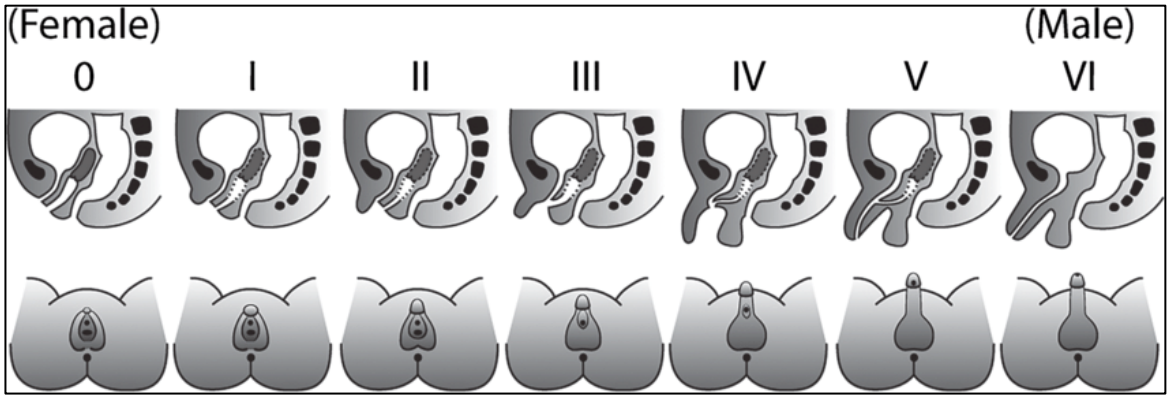

Fig. 5. Grades of Prader scale for XX patients with congenital adrenal hyperplasia [16].

serve sensation and sexual function. Complications of the above-mentioned surgical treatment include vaginal stenosis, which may require additional surgery, typically as a teenager [10], fistulas, urinary incontinence, recurrent urinary tract infection and impaired clitoral sensitivity. In addition, they require lifetime glucocorticoid therapy to minimize the ever-present risk of hyperandrogenemia.

In 46XX CAH with severe virilization and a complete penile urethra, Prader V genitalia (Fig. 5), female sex of rearing is advisable when the diagnosis is made in the neonatal period. A male sex of rearing is reasonable for those whom the diagnosis was made after the neonatal period; with successful reported outcomes [11, 12]. Surgical feminization surgery is challenging due to high insertion of the vagina close to the bladder neck; Robotic and laparoscopic abdominal approaches to the high urogenital sinus have avoided the need for a temporary diverting colostomy and/or the anterior sagittal transrectal approach procedure [13-15]. In those raised as males, they may undergo hypospadias repair in infancy. Treatment with a gonadotropin-releasing hormone (GnRH) analog can be considered before puberty so that a hysterectomy and oophorectomy deferred until later in adolescence when the patient can affirm their gender identity.

In the second case scenario, the patient clinically had a severe form of hypospadias, left impalpable testis and the right testis was palpable in the scrotum. Surgical findings were left sided fallopian tube, atrophic left hemi-uterus and ovary; and the testis was identified in the right-sided inguinal exploration. The ovarian biopsy was consistent with left ovarian tissue and the testicular biopsy was consistent with right testicular tissue. Testosterone and AMH levels were normal. Karyotype showed 46XY chromosome and FISH for SRY probe confirmed Y chromosome in 100% of the analyzed metaphases. The above information most likely fits the condition of ovotesticular DSD (previously known as "true" hermaphroditism). The other differential diagnosis is mixed gonadal dysgenesis (MGD) but it's less likely in this case because Mullerian structures and testicular tissue are usually seen on the same side in MGD; the dysgenetic testicular tissue in MGD secretes inadequate amounts of AMH which may lead to preservation of Mullerian structures on the side of testicular tissue.

Ovotesticular DSD has an incidence of < 10% of all DSD. Out of the total diagnosed ovotesticular disorder cases, 46 XX chromosome is seen in 59.5% of cases and 12.3% have 46 XY chromosome [17]. In this condition, different gene mutation causes both male and female gonadal tissue (testis, ovary, or ovotestis) as well as male and female internal and external structures to coexist. The testes are most often found on the right side. Ovaries are most often found on the left side, and ovotestes -in which both ovarian follicular and testicular tubular tissue are present- can occur on either side. The diagnosis is made based on histology. The phenotype depends on the degree of both testosterone and AMH. Data from small case series suggest that patients reared in either sex can be satisfied with their sex assignment [18, 19] but that gender dysphoria also may occur [20]. Surgery involves the removal of the discordant ovarian tissue if a male sex of rearing is assigned and the removal of testicular tissue if a female sex of rearing is assigned. Gonadectomy may be necessary if ovotestis present to prevent discordant

secondary sex characteristics. The resultant testis cannot produce sperms if it was an XX karyotype due to the lack of y chromosome but the resultant ovotestis may produce oocytes in some cases.

In the third case scenario, the child clinically had a phallic length of 2.2 cm (in a typical XY term infant, penile length is ≥ 2.5 cm [21]), mid penile hypospadias, gonads impalpable bilaterally with underdeveloped scrotum. No Turner's stigmata were visualized. Karyotype was consistent with 46XY chromosome and was positive for SRY gene. Laboratory investigations showed higher than normal levels of basal testosterone and dihydrotestosterone. Cysto-genitoscopy revealed low insertion of the vagina into the urethra. Laparoscopic findings revealed a uterus with a bilateral ovary-looking gonad. No testes were seen. Biopsy from bilateral gonads was sent and histopathology was consistent with testicular tissue from both gonads. Based on the above findings and information, a diagnosis of partial gonadal dysgenesis was made.

XY gonadal dysgenesis is defined by failure of testicular development, resulting in underproduction of testosterone (which is the function of Leydig cell) and underproduction of anti-mullerian hormone (which is the function of Sertoli cell). Anti-mullerian hormone (AMH) causes Mullerian duct regression. Thus, decreased AMH secretion can result in fully or partially developed Mullerian duct structures [22, 23]. Gonadal dysgenesis can be classified as either complete (pure) gonadal dysgenesis (CGD) or partial (mixed) gonadal dysgenesis (PGD) depending on the gonadal morphology [24, 25]. In complete gonadal dysgenesis, there is complete failure of testicular development and thus, patients have a completely female phenotype with typical female external genital appearance due to the lack of any gonadal steroid production with normal Müllerian structures and bilateral streak gonads [26]; If gonadal biopsy is performed, gonadal histology would reveal the presence of bilateral dysgenetic streak gonads. In partial gonadal dysgenesis, there is partial but incomplete gonadal development and can result in a wide range of testicular function and thus, a wide range of phenotypes ranging from isolated infertility, to hypospadias, to an atypical genital appearance, to clitoromegaly. The Mullerian structures may be normal, hypoplastic, or absent.

The most common karyotype seen in PGD is 45X/46XY but 46XY can also be seen. Gonadal histology may reveal either bilateral dysgenetic testes or one streak gonad (usually the left side) and a contralateral dysgenetic or normal-appearing testis (usually the right side). Most individuals with mixed gonadal dysgenesis will have a male gender identity; This is consistent with the moderate level of genital virilization, the presence of a Y chromosome, and the in-utero exposure to higher levels of androgen. The genes commonly involved in XY gonadal dysgenesis include NR5A1 loss-of-function, SRY loss-of-function, WT1 mutation, NR0B1 Duplication and AMH gene mutation.

Regarding the treatment of gonadal dysgenesis, patients with XY CGD are recommended to have bilateral gonadectomy at the time of diagnosis given the high risk of gonadoblastoma reported as 15-35% [27-29]; in patients with XY PGD with nonscrotal gonads that cannot be repositioned surgically into a scrotal position are recommended to have bilateral gonadectomy. Patients with XY PGD with scrotal gonads being reared as males should undergo routine monitoring with self-examination for development of malignancy. In patients with XY PGD who are reared as males with mild under-virilization and gonads that can be repositioned into the scrotum via orchidopexy, one prepubertal gonadal biopsy is recommended at the time orchidopexy is performed and one post-pubertal gonadal biopsy to monitor for malignancy [30]; a normal gonadal biopsy does not completely rule out the presence of a small tumor. Hypospadias surgery is performed at 6 to 15 months of age [31]. Preoperative androgen treatment should be considered if penile size less than average. The Mullerian remnant (hemiuterus) is typically removed at the same time as the streak gonad -if present.

CONCLUSION

Individuals with a congenital discrepancy between the appearance of their external genitalia and gonadal and chromosomal sex are classified as having disorders of sex development (DSD). These disorders are classified into three main categories based on the karyotype; XX DSD (i.e. CAH, ovotesticular DSD), XY DSD (i.e. gonadal dysgenesis, abnormal androgen synthesis or response), and sex chromosome DSD (i.e. mosaicism, chimerism). Laboratory investigations, karyotype, ge-

netic analysis, imaging, diagnostic surgery and histopathology, all aid in diagnosing the specific type of DSD. Decisions about sex of rearing should be based on clinical outcomes for the specific type of DSD, fertility potential and the degree of virilization. The treatment is surgical and/or medical depending on the type of DSD. Several DSD are associated with variable risks for gonadal malignancy and require specific monitoring and management.

Authors' Contribution

Study Conception: SAK; Study Design: SAK; Supervision: RPK, MJS; Funding: RPK, MJS, SAK, MSB; Materials: SAK, MSB, RPK, MJS; Data Collection and/or Processing: SAK, MSB; Statistical Analysis and/or Data Interpretation: SAK, RPK; Literature Review: SAK, RPK; Manuscript Preparation: SAK and Critical Review: RPK, MJS, SAK, MSB.

Ethical approval

The study was approved by The Royal Hospital Ethical Committee, Muscat, Oman.

Informed Consent

Written informed consent was obtained from the families of patients for publication of this case series and any accompanying images or data.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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