Case Report

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Karyotype Determination is Important in the Differential Diagnosis of Proximal Hypospadias

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Proximal hypospadias, a clinical diagnosis following the location of the urethral meatus, is classified into the proximal shaft, penoscrotal, scrotal, and perineal types. In most instances, hypospadias is considered an isolated anatomical defect. However, between 2014 and 2018, three patients were noted to have sexual development disorders initially misdiagnosed as isolated proximal hypospadias at a single tertiary referral hospital. The first patient presented with penoscrotal-type hypospadias and the final diagnosis was congenital adrenal hyperplasia with karyotyping 46 XX. The second patient, who had the presentation of scrotal-type hypospadias with left testis and right ovary, was finally diagnosed as having 46 XY ovotesticular disorder of sexual development. The third patient with manifestation of normal male genitalia except for penoscrotal-type hypospadias was later diagnosed with 46 XX testicular disorder of sexual development. Therefore, karyotyping should be performed in all patients who present with proximal hypospadias to prevent misdiagnosis.

Key words: proximal hypospadias, disorder of sexual development, karyotype

Introduction

Hypospadias is the second most common congenital anomaly in males with incidences varying from 0.3% to 0.7% in live male births.[1] It is characterized by proximal displacement of the urethral opening, penile curvature, and a ventrally deficient hooded foreskin. It presents as distal and middle hypospadias in about 80% of all cases, in which the urethral meatus in distal hypospadias is located at the glans, corona of the glans penis or distal penile shaft while it is at the midshaft of the penis in middle hypospadias. Such conditions are considered mild and isolated anatomical defects. The remaining 20% are proximal hypospadias, in which the urethral meatus is located at the midshaft, proximal penile shaft, junction of penis and scrotum, and scrotum or perineum. Compared with distal and middle hypospadias, proximal hypospadias is often more complex and associated with other organ system anomalies (e.g., congenital cardiac

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disease or imperforate anus).[1] In some patients, hypospadias may be accompanied by a more complex disorder of sex development (DSD).[1,2] Previous studies showed that DSD should be considered when patients present with proximal hypospadias and one or more coexisting anomalies including micropenis, undescended/impalpable testes, and penoscrotal transposition/bifid scrotum.[3] Between 2014 and 2018, three DSD cases would have been misdiagnosed as simple proximal hypospadias if karyotyping had not been performed.

Case Report

The current study retrospectively reviewed three cases of proximal hypospadias with DSD between 2014 and 2018 at a tertiary referral hospital. The clinical presentations, results of karyotyping, and information on medical/surgical treatments of the three patients are summarized in Table 1.

Case 1

Images in Clinical Medicine of the New England Journal of Medicine reported a case in 2015.[4] A 4-day-old infant born to a 25-year-old G3P1SA2 mother after 39 weeks and 3 days of uncomplicated pregnancy via normal spontaneous vaginal delivery with a body weight of 2,990 g. Despite ambiguous genitalia, the baby was regarded as a boy with bilateral undescended testes and penoscrotal hypospadias (Fig. 1). No family history of similar presentations or known genetic disorders was noted. The neonate had sinus tachycardia without hypotension, and congenital adrenal hyperplasia was suspected. Laboratory evaluation revealed an elevated potassium level of 7.4 mmol/L (normal range, 3.5 – 5.3 mmol/L), a low sodium level of 125 mmol/L (normal range, 135 – 148 mmol/L), an elevated 17-hydroxyprogesterone

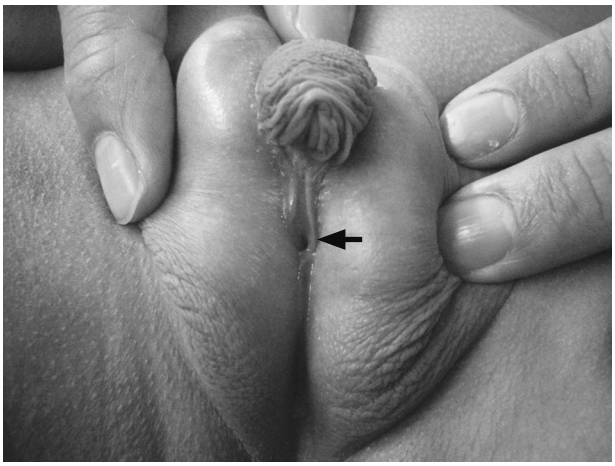

Fig. 1 Case 1: Urethral orifice (black arrow).

Table 1. Case series.

Case number	1	2	3
Karyotyping	46 XX	46 XY	46 XX
Genital presentation	Penoscrotal type hypospadias Bilateral undescended testes	Scrotal type hypospadias Bilateral undescended testes (Left palpable testis)	Penoscrotal type hypospadias Bilateral retractile testes
Accompanied fingings	Tachycardia	Vaginal orifice	None
Sonographic fingings	Bilateral adrenal hypertrophy	-	No ovaries and uterus
Laparoscopic fingings	-	Uterus and right ovary	No ovaries and uterus
Pathological fingings	-	-	Bilateral testicular tissue
Final diagnosis	Congenital adrenal hyperplasia (CAH)	Ture hermaphroditism (46 XY ovotesticular DSD)	46 XX testicular DSD with SRY-negative
Medical treatment	Glucocorticoid and mineralocorticoid	-	-
Surgical treatment	Repair of the urogenital sinus Clitoroplasty Vaginoplasty	Orchiectomy Labioplasty Clitoral recession	Island flap urethroplasty

level of 196.0 μg/L (normal range, 0.5 – 2.4 μg/L), and a testosterone level of more than 15.0 ng/mL (normal range, 0.1 – 0.8 ng/mL). Abdomen ultrasonography demonstrated bilateral adrenal hypertrophy without visible testes, while chromosomal analysis showed 46 XX karyotypes. Salt-wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency in a female infant was diagnosed. The ambiguous genitalia, characterized by hypertrophy of the clitoris and labia majora as well as the presence of a urogenital sinus, may resemble hypospadias with cryptorchidism in males. Consequently, medical treatments including correction of electrolyte abnormalities, intravenous fluid administration, and glucocorticoid and mineralocorticoid replacement were initiated. At two years old, the patient underwent complex surgical reconstruction, including repair of the urogenital sinus, clitoroplasty, and vaginoplasty. The patient has regular follow-ups and is doing well with glucocorticoid and mineralocorticoid replacement therapy.

Case 2

A two-day-old neonate, born via Cesarean section, was sent to our hospital. The gestational age of the patient was 37 weeks plus 2 days with a body weight of 3,260 g and a maternal status of G10P5A5. The Apgar score was 8′ and 9′ at the first and fifth minutes, respectively. No known family history of genetic disorders was noted. Scrotal-type hypospadias and bilateral undescended testes were found after birth. Left inguinal hernia was also noted, for which left inguinal herniorrhaphy and orchiopexy were performed. The patient was readmitted for surgical correction of scrotal-type hypospadias six months later. However, one orifice was accidentally noted at the dorsal side of the urethral orifice while the operation was being prepared (Fig. 2). Diagnostic laparoscopy revealed the presence of the uterus and right-side ovary within the peritoneal cavity without right testis tissue or left ovarian tissue. A chromosome examination showed a 46 XY karyotype. Under the impression of true hermaphroditism, the patient was assigned a female gender and received orchiectomy, labioplasty, and clitoral recession based on the parents' decision.

Case 3

A two-month-old infant was sent to our pediatric surgical department for proximal hypospadias. The patient, who was born via Cesarean section due to prolonged labor at a gestational age of 40 weeks and 2 days with a birth weight of 3,975 g, was found to have ambiguous genitalia with penoscrotal-type hypospadias and bilateral retractile testes (Fig. 3). A chromosome study showed a 46 XX karyotype

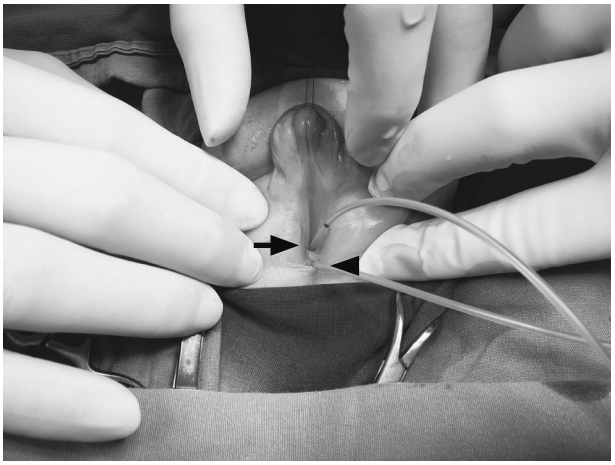

Fig. 2 Case 2: Urethral orifice (black arrow); vaginal orifice (black arrowhead).

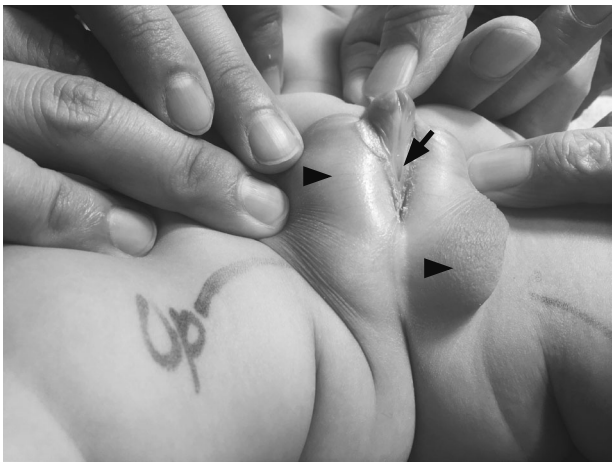

Fig. 3 Case 3: Urethral orifice (black arrow); testes (black arrowhead).

with absence of uterus and ovary on abdominal sonography. Renal sonography showed no obvious lesion. The patient was brought to the pediatric surgical outpatient department for a second opinion and further surveys. Repeated chromosome study confirmed a 46 XX karyotype and the sex-determining region of Y-chromosome (SRY) screening showed no SRY detection. Laparoscopic evaluation demonstrated the absence of uterus and ovaries. Biopsy of bilateral testes showed normal testicular structure without definite ovarian tissue. Therefore, the diagnosis of true hermaphroditism with chromosome 46 XX karyotypes, known as 46 XX testicular DSD, was confirmed. Island flap urethroplasty was then performed at 10 months old.

Discussion

DSD is defined as individuals with congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex.[3] Ambiguous genitalia, which are present in most of these patients,[5] have varied etiologies with 46 XX DSD being the most common especially CAH of the salt-wasting type.[6] In some females, the vagina fuses with the urethra to form a urogenital sinus because of excess androgens. The hypertrophic change of the clitoris and labia majora contributes to the false impression of a penis and bifid scrotum, resembling the penoscrotal- or perineum-type hypospadias with undescended testis in males.[3] Moreover, more than 75% of children with CAH present with a salt-wasting variety at birth. These newborns have a high mortality rate for delayed diagnosis and treatment.[6]

46 XX DSD presents as one of three phenotypes. The first one is XX testicular DSD with normal genitalia. In addition, 85% of the cases have normal male internal and external genitalia and are usually diagnosed after puberty because of hypogonadism, gynecomastia, and/or infertility. The second phenotype is XX testicular DSD with ambiguous genitalia identified at birth by external genital ambiguities (e.g., micropenis, cryptorchidism, or hypospadias). The last one is XX ovotesticular DSD with internal and external genital ambiguities detected at birth or histologically.[7] Approximately 80% of the patients with 46 XX testicular DSD are SRY-positive and usually have a normal male phenotype at birth. Other SRY-negative 46 XX males exhibit different degrees of masculinization. In addition, 46 XX SRY-negative individuals with complete masculinization are rare and usually exhibit phenotypic differences. Regardless of the results of SRY screening, these patients are often infertile.

Ovotesticular DSD is an uncommon condition in which about 90% of patients have a 46 XX karyotype. However, some cases of 46 XY ovotesticular DSD have also been reported. Although the presentations vary, ranging from normal males to normal females, with or without palpable gonads, the most common presentation is abnormal external genitalia. Genital ambiguity with mild clitoromegaly, chordee, hypospadias, and cryptorchidism may be present. If left untreated and the patient is raised as a female, features of hyperandrogenism (e.g., voice changes and clitoral enlargement) would be evident during adolescence. Those raised as males may present with hypospadias and undescended testes as well as experience significant estrogenization at puberty.[8] Moreover, the risk of gonadal tumors is low in the dysgenetic testicular tissue and appears to be about 2.6%. Therefore, the biggest issue for ovotesticular DSD is gender determination, for which no consensus currently exists regarding the indications or timing of surgery because these individuals sometimes develop a different gender identity as they enter adolescence. A meta-analysis in 2020 showed that the overall prevalence of gender identity disorder was 15% among those with DSD. Nevertheless, it varies with the type of DVD. It is important to

realize that each patient diagnosed with DSD is unique and warrants multidisciplinary care and long-term psychosexual support.[9]

The reported prevalence of a specific DSD diagnosis in 8.5% – 11.4% of patients presenting with proximal hypospadias[3,10] may be underestimated. In these studies, they found that micropenis, undescended/impalpable testes, or penoscrotal transposition/bifid scrotum more commonly occurred in proximal hypospadias patients with DSD. The presence of bilaterally descended testes does not preclude the possibility of DSD,[3] which was noted in the third patient. Moreover, some patients that had proximal hypospadias with streak gonads have been reported to develop gonadal germ cell neoplasms despite the low risk.[10] Therefore, early DSD diagnosis is important. The results of the current study suggest that karyotyping should be performed in all patients who present with proximal hypospadias for preventing misdiagnosis.

Author Contributions

Study design, Po-Jui Ko and Ming-Lun Yeh; Data collection, Chih-Jong Tsai, Po-Jui Ko, Ming-Lun Yeh and Chih-I Chen; Data interpretation, Chih-Jong Tsai, Po-Jui Ko and Ming-Lun Yeh; Manuscript preparation, Chih-Jong Tsai; Literature search, Chih-Jong Tsai. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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