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Original Article

Proximal hypospadias and *46XY* disorder of sex development; which patient with hypospadias needs to be investigated?

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Abstract

Aim: This study examines the distribution of genital abnormalities based on physical examination of our patients with *46, XY* disorders of sex development (*46, XY* DSD), and aims to define severity and frequency of hypospadias in *46, XY* DSD. Hypospadias is a relatively prevalent congenital anomaly. Although genetic, environmental and hormonal factors are considered to be responsible, etiology is not clarified in several hypospadias cases.

Materials and Methods: Clinical, laboratory and genetic records of all cases with *46, XY* DSD, who were evaluated by the sex determination monitoring board were retrospectively reviewed. In the diagnosis, hypospadias cases were examined in terms of the place of hypospadias and coexisting other external genital findings.

Results: There were 72 patients with *46, XY* DSD. 5-α reductase deficiency [n=32 (44.4%)] was the most commonly encountered diagnosis followed by androgen insensitivity syndrome [n=26, (36.1%)]. Proximal hypospadias were presented in 44.4% (n: 32) of the cases and only 6 of them (18.8%) were isolated hypospadias. In 81.2% of these cases, at least one of the anomalies such as cordi, bifid scrotum, undescended testis and micropenis accompanied proximal hypospadias. None of the distal hypospadias cases were referral clinic finding.

Conclusions: 46 XY DSD is a heterogeneous group of patients with a varying age of presentation and a diverse clinical profile. It can be stated that proximal hypospadias is the most common referral clinic finding of *46, XY* DSD, and the risk of *46, XY* DSD increases with the intensifying degree of hypospadias and the presence of coexisting genital abnormalities such as cordi, bifid scrotum, undescended testis and micropenis.

Keywords: *46, XY* DSD; disorders of sex development; etiology; proximal hypospadias

INTRODUCTION

Male sex development is a complex and multiple-stage process dependent on genetic and hormonal control. In order for the transformation of bipotential gonad into testicle and differentiation of male internal and external genitalia in the presence of testicular hormones, a precise network of molecular events is required; genetic and endocrine factor disorders contributing to testicular development, hormone synthesis and effect lead to *46, XY* disorders of sex development (*46,XY* DSD). *46, XY* DSD covers a wide phenotype range from complete female external structure to male external genitalia with slight virilization defect such as hypospadias (1,2).

Hypospadias is a relatively prevalent congenital anomaly seen in nearly every 200-300 live birth (3,4). It is a severe form of which 20% is defined as proximal hypospadias (5). Although genetic, environmental and hormonal factors are considered to be responsible, etiology is not clarified in several hypospadias cases (6). Some previous studies state that proximal hypospadias often shows genital abnormalities such as bifid scrotum undescended testicle and microphallus, and can be an indicator of *46, XY* DSD (5).

This study examines the distribution of isolated hypospadias or coexisting additional genital abnormalities based on clinical referrals of our patients with *46, XY* DSD, and aims to define severity and frequency of hypospadias in *46, XY* DSD, and determinate which hypospadias patients should be investigated.

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MATERIALS and METHODS

Medical records of all cases with disorders of sex development between 2009-2016 in pediatric endocrinology clinic, evaluated by the sex determination monitoring board were retrospectively reviewed. The patients were classified as adopted by the Consensus Conference (7). All patients with diagnosis of *46, XY* DSD were included the study. The cases diagnosed with 46, XX DSD and sex chromosome DSD were excluded. Referral complaints, clinical findings and external genital masculinization scores of all cases were determined and proper diagnostic evaluations (radiological and serological) were carried out. Phenotypes of the patients with to *46, XY* DSD were classified by sinnecker classifications. For defined genitalia of patients as type 1 and type 2 (male and male predominant) the term hypospadias and for type 3, the term ambiguous was used (8). In the diagnosis, hypospadias cases were examined in terms of the place of hypospadias and coexisting other external genital findings. All records were reviewed in order to verify the diagnosis of the patients under monitoring. Karyotype analysis, follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), estradiol (E2), cortisol, androstenedione (A), dehidroepiandrostenedione-sulphate (DHEAS-SO4), adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), dihydrotestosterone (DHT), anti-Mullerian hormone (AMH), serum electrolytes, urine analysis and routine tests involving abdominal and pelvic ultrasounds were carried out for new patients. LH, FSH, T, E2, cortisol and DHEAS-SO4 levels were studied in ADVIA Centaur XP (SIEMENS) device with chemiluminescence method; ACTH, A, 17-OHP, DHT levels were measured using liquid chromatography/tandem mass spectrometry (LC-MS/MS) method, AMH was measured by enzyme immunoassay (Ansh Labs, AMH/MIS ELISA kit). Karyotype analyses were carried out by examining 100 metaphases with cytogenetic analysis of peripheral blood samples. For cases that passed the mini puberty period and in prepubertal period, chorionic gonadotropin (hCG) test was carried out with the aim of evaluating the function of the testicular tissue. 1500 IU/m2 hCG (Pregnyl®) was applied for consecutive 3 days with 24 hours intervals. Testosterone level> 100 ng / ml at 24 h after the test was considered to be sufficient testosterone synthesis (9). Testosterone, androstenedione and dihydrotestosterone levels were evaluated before the test and 24-48 hours after the test. Testosterone/Androstenedione (T/A) and testosterone/DHT (T/DHT) ratios were calculated in order to define 17β- hydroxysteroid dehydrogenase deficiency and 5α-reductase deficiency, respectively. Laparoscopy was carried out in required cases and gonad biopsy was taken from 5 cases. Following sex determination, gonadectomy was carried out in required cases.

For 5α-reductase deficiency diagnosis, testosterone/DHT (T/DHT) ratio>12, exclusion of other diagnoses in additional hormonal tests and showing the absence of female internal genital organs in ultrasonographic examinations were looked for as criteria, moreover mutation analyses were carried out in SRD5A2 gene in these cases.

Androgen insensitivity syndrome (AIS) was diagnosed in under virilized males who had normal T and DHT response to hCG stimulation and absence of Müllerian structures. Those with normal female external genitalia were considered as complete AIS (CAIS) and the rest - as partial AIS (PAIS). Androgen receptor (AR) gene analysis was performed in patients with PAIS-like.

The absence of female internal genitalia, besides the exclusion of other diagnoses, due to the finding of Testosterone/Androstenedione (T/A) <0,8, in cases thought to have the diagnosis of 17β-hydroxysteroid dehydrogenase deficiency, mutation analyses were carried out in HSD17B3 gene.

In cases without female internal genitalia as well as ambiguous genitalia, diagnosed with hyponatremia and hyperpotassemia in neonates, 3β-hydroxysteroid dehydrogenase deficiency was diagnosed by high measurements of androgen precursors. HSD3B2 gene analysis was carried out in order to verify the diagnosis.

Persistent Müllerian duct syndrome (PMDS) was defined as normal male external genitalia, normal response to hCG, and presence of Müllerian structures detected by ultrasound.

The SPSS software version 20.0 (SPSS, Inc., Chicago, Il, USA) were performed. Continuous data were given as the mean ± SD or median (25^{th}; 75^{th} percentile) and categorical variables were given as number (percentages).

Families of each participant provided written informed consent, and all studies were conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the local ethical committee (Sultangazi Haseki Training and Research Hospital, no: E-2020-57).

RESULTS

A total of 72 cases diagnosed with *46, XY* sex development disorder, were included in the study. The median age was 1.05 (0.2-9.8) years. Referral clinical findings were as follows: proximal hypospadias in 44.4% (n=32) of the cases and 6 of these 32 cases were isolated. In 24 cases with proximal hypospadias had at least one additional external genital anomaly (micropenis, undescended testicle, bifid scrotum, chordee); complete female external genitalia in 26.4% (n=19) (delayed puberty in 10, discovery of gonads during inguinal hernia operation in 9) of the cases; ambiguous genitalia in 9.7% (n=7) of the cases; clitoromegaly in 5.5% (n:4) of the cases; micropenis ± undescended testicle in 6.9% (n=5) of the cases; virilization in puberty in 4.2% (n=3) of the cases; undescended testicle in 2.8% (n=2) of the cases. None of the distal hypospadias cases were referral clinic finding.

Table 1. Diagnostic distribution of 72 cases with *46, XY* disorders of sex development and referral clinical findings

Diagnosis and referral clinical	n (%)
5α-reductase deficiency	**32 (44.4%)**
Proximal hypospadias	5 (15.6%)
Proximal hypospadias + undescended testicle	4 (12.5%)
Proximal hypospadias + micropenis	6 (18.8%)
Proximal hypospadias + bifid scrotum	3 (9.4%)
Proximal hypospadias + micropenis+ undescended testicle	1 (3.1%)
Micropenis	2 (6.3%)
Micropenis + undescended testicle	2 (6.3%)
Ambiguous genitalia	2 (6.3%)
Clitoromegaly	2 (6.3%)
Female external genitalia + palpable gonad	3 (9.4%)
Virilization in puberty	2 (6.3%)
Complete androgen insensitivity	**10 (13.9%)**
Delayed puberty	7 (70%)
During inguinal hernia operation	3 (30%)
Partial androgen insensitivity	**16 (22.2%)**
Proximal hypospadias	1 (6.3%)
Proximal hypospadias + undescended testicle	2 (12.5%)
Proximal hypospadias + micropenis	3 (18.8%)
Proximal hypospadias + micropenis + undescended testicle	1 (1.3%)
Proximal hypospadias + bifid scrotum	3 (18.8%)
Micropenis + undescended testicle	1 (6.3%)
Ambiguous genitalia	3 (18.8%)
Clitoromegaly	1 (6.3%)
Virilization in puberty	1 (6.3%)
Gonadal dysgenesis Delayed puberty	**3 (4.2%)**
17β-hydroxysteroid dehydrogenase deficiency	**3 (4.2%)**
Clitoromegaly	1
Female external genitalia (during inguinal hernia operation)	2
Leydig cell hypoplasia Ambiguous genitalia	**1 (1.4%)**
3β hydroxysteroid dehydrogenase deficiency	**2 (2.8%)**
Proximal hypospadias + bifid scrotum	1
Ambiguous genitalia	1
Isolated mullerian inhibin factor deficiency Undescended testicle	**2 (2.8%)**
Ovotesticular *46, XY* disorders of sex development	
Inguinal hernia operation	1
Proximal hypospadias + undescended testicle	1
Denny-Drash syndrome	**1 (1.4%)**
Proximal hypospadias + undescended testicle	

When analyzed according to diagnostic distribution; referral diagnostic median ages of 32 (44.4%) cases with 5α-reductase deficiency was 0.85 (0.12-4.77) years; in referral physical examinations, 59.3% (n=19) of the cases with 5α-reductase deficiency had proximal hypospadias ± additional external genital anomaly (micropenis, undescended testicle, bifid scrotum, chordee). In pubertal cases, basal testosterone syntheses were normal values by age and male sex, in prepubertal cases, after hCG test testosterone syntheses were sufficient (154,4±61,1 ng/ml)and T:DHT ratios were above 12. In 29 (%90.6) of the cases, mutation was detected in 5 SRD5A2 gene.

In 38.8% (n:28) of all cases determined defect in androgen actions. The median age of 10 (13.8%) cases diagnoses with complete androgen insensitivity (CAIS) was 13.9 (13-15.3) years. Referral complaints were palpable gonad in

inguinal region (n:3) and puberty delay (n:7). Testosterone syntheses were sufficient (415,3±93,6 ng/ml). The median age of 16 (22.2%) of the cases diagnoses with partial androgen insensitivity (PAIS) was 0.7 (0.2-2.7) years. In referral physical examinations, 62.5% (n=10) of the cases with PAIS had proximal hypospadias ± additional external genital anomaly. Testosterone syntheses were sufficient (176.2±124,1 ng/ml) and T:DHT ratios were <12. In 12 (%75) cases with PAIS, AR gene mutation were detected.

Referral complaints of the 3 (4.1%) cases with complete gonadal dysgenesis (Swyer syndrome) diagnosis were puberty delay with complete female external genitalia. Basal testosterone values and testosterone response to hCG stimulant test were low. LH (28.9, 44.3 and 31.8 mIU/l), FSH (78.4 and 99.1 and 67.3 mIU/l) values were found to be high. In all cases, the diagnosis was verified by histopathological tests.

Due to the determination of T:DHT ratio as <12 and T:A ratio as <0,8 in the hormonal evaluation of the referral cases with complete female genitalia with gonads palpable in inguinal region (n=2) and clitoromegaly (n=1), 2 different homozygote mutation were determined in HSD17B3 gene analysis. These cases were diagnosed as 17β-hydroxysteroid dehydrogenase deficiency.

In the hormonal evaluation of 2 (2,8%) cases with clitoromegaly (n:1), proximal hypospadias + bifid scrotum (n:1) and hyponatremia, hyperpotassemia complaints, 3β-hydroxysteroid dehydrogenase deficiency was diagnosed due to very high measurements of ACTH and precursor steroids (DHEA-SO4, 17-OHP, 17-OH pregnanolone).

Two (2.8%) cases were diagnosed with Muller structures during operation due to undescended testicle. Gonad biopsy result was determined as compatible with the testicle tissue. Cases with very low anti-Mullerian hormone levels were diagnosed with PMDS due to AMH deficiency.

In one case with male external genitalia whose operated because of inguinal hernia in neonate was detected of fallopian tubes and over-like gonads. One case referred with ambiguous genital. Testosterone synthesis defect was determined in hormonal evaluation. These cases (n:2, 2.8%) was diagnosed as ovotesticular DSD due to the detection of both testicle and ovarian tissue in gonad biopsy.

One case diagnosis with leydig cell hypoplasia referred with ambiguous genitalia. Testosterone synthesis defect was determined in hormonal evaluation. Gonad biopsy resulted as testicle tissue without leydig cell. Genetic analysis studies of LHR gene are still in progress.

In the hormonal evaluation of the case referred due to proximal hypospadias + undescended testicle, testosterone synthesis was sufficient. Renal biopsy of the case developing renal failure in the follow up was determined to be compatible with the focal segmental glomerulosclerosis. Denny-Drash syndrome was diagnosed.

Referral clinical findings of all cases with *46, XY* DSD are presented in Table 1 according to diagnostic distribution.

Considering diagnostic distribution of the cases with proximal hypospadias, it was detected that the majority of the cases (90.6%, n:29/32) formed 5α-reductase deficiency and PAIS and all of the cases with isolated hypospadias remained in this group Table 2.

Table 2. Diagnostic distribution of the cases with and without proximal hypospadias in *46, XY* disorders of sex development phenomena

Cases with Proximal Hypospadias (n:32, 44.4%)		Cases without Proximal Hypospadias (n:40, 54.6%)	
5α-reductase deficiency	59.4% (n:19)	5α-reductase deficiency	32.5% (n:13)
PAIS	31.3% (n:10)	CAIS	25% (n:10)
Ovotesticular	3.1% (n:1)	PAIS	15% (n:6)
3β-HSD deficiency	3.1% (n:1)	17β-HSD deficiency	7.5% (n:3)
Danny-Drash syndrome	3.1% (n:1)	Gonadal dysgenesis	7.5% (n:3)
		Isolated MIF deficiency	5% (n:2)
		3β-HSD deficiency	2.7% (n:1)
		Ovotesticular *46, XY* DSD	2.5% (n:1)
		Leydig cell aplasia	2.5% (n:1)

PAIS; Partial androgen insensitivity, CAIS; Complete androgen insensitivity, 3β-HSD deficiency; 3β hydroxysteroid dehydrogenase deficiency, 17β-HSD deficiency; 17β-hydroxysteroid dehydrogenase deficiency, Isolated MIF deficiency; Isolated mullerian inhibin factor deficiency, DSD; disorders of sex development

DISCUSSION

In this study, we examined the etiology and clinic profiles of 72 cases diagnosed with *46, XY* DSD, and defined the frequency and importance of hypospadias in *46, XY* DSD. 5α-reductase deficiency was the most commonly encountered diagnosis followed by androgen insensitivity syndrome. We showed that nearly half of the cases diagnosed with *46, XY* DSD referred with proximal hypospadias. The most (81.2%) of cases with proximal hypospadias had at least one additional external genital anomaly.

In male sex development, bipotential gonad transforms into testicle in the presence of SRY gene on Y chromosome (10). Fetal hormones produced by the formed testicular tissue ensure the formation of internal and external organs. While testosterone released from fetal testicle leydig cells ensure the development of internal genitals (vas deferens, epididymis, and vesiculo seminalis), anti-mullerian hormone released from sertoli cell causes irreversible regression of muller structures (11). On the other hand, the development of external genitalia is realized by the transformation of testosterone into 5α reductase enzyme and dihydrotestosterone, a more potent steroid.

There are a number of reasons for *46, XY* DSD. They can be roughly categorized into three groups as development defects of testicle, testosterone development and synthesis defects and androgen insensitivity syndrome. There are a limited number of studies evaluating the diagnostic distribution of *46, XY* DSD. Al-Jurayyan et al., in their study, diagnosed androgen insensitivity syndrome in 16 of the 56 cases, and 5α-reductase deficiency in 9 cases (12). Similarly, Abdullah et al. and Joshi et al. reported androgen insensitivity syndrome as the most common diagnosis in their studies (13,14). In the present study, unlike the previous findings, 5α-reductase deficiency was reported as the most common diagnosis and androgen insensitivity syndrome as the second most common diagnosis. This difference was attributed to the frequent consanguineous marriage and the fact that OR transitive diseases are more common in consanguineous marriage. Similar to the present study, Chauhan et al., in their study evaluating 40 cases, reported 5α-reductase deficiency (40%) as the most common diagnosis (15). Although studies have shown that T/DHT ratio was significantly lower compared to 5α-reductase deficiency in androgen insensitivity syndrome, it can be difficult to carry out a definitive diagnosis of these two diseases with clinical and hormonal findings, and mutation analyses may be needed for the verification of this diagnosis.

46, XY DSD covers a wide phenotype range from complete female external structure to male external genitalia with slight virilization defect such as hypospadias. Hypospadias is the most commonly seen congenital anomaly and its etiology has not been clearly determined. Its relation to the deficiency in the tubulization of urethane of damaged androgen stimulation in animal models (16,17). This relation of the development of hypospadias and undescended testicle with androgen is related to the deterioration in androgen axis and DSD (18). However, it is still unknown to research which patients with proximal hypospadias in terms of DSD and to what extent these researches should be carried out. In their study with 102 proximal hypospadias cases, Palmer et al. diagnosed *46, XY* DSD in 17% of the cases, mixed gonadal dysgenesis in 6 cases, partial androgen insensitivity in 5 cases, leydig cell hypoplasia in 1 case, *46, XXY* Klinefelter in 1 case, other chromosomal disorders in 4 cases; and 88% of 17 cases presented with penoscrotal or hypospadias perineal as referral clinical finding, in 47% undescended testicle coexisted (19). In their study, Sekaran et al. diagnosed *46, XY* DSD in 30% of the 63 proximal hypospadias cases, and divided these cases into two groups as with or without undescended testicle; the ratio of the cases diagnosed with *46, XY* DSD was significantly higher than the group coexisting with undescended testicle (20). Similarly, another study evaluating 63 proximal hypospadias cases reported that of these 31% cases with determined etiologic cause, 17% was diagnosed with complex genetic syndromes, 9,5% with sex chromosome aberration, 1 with androgen insensitivity, 2 with leydig cell hypoplasia, 2 with 17β-hydroxysteroid dehydrogenase deficiency and 1 with 5α-reductase deficiency (5). Previous studies focused on incidence rates of DSD in hypospadias while in our study, we defined the relationship between *46, XY* DSD and proximal hypospadias after the evaluation of referral clinic findings of the cases diagnosed with *46, XY* DSD. We showed that nearly half of the cases diagnosed with *46, XY* DSD referred with proximal hypospadias, and 81.2% of these cases coexisted with at least one abnormalities such as chordee, bifid scrotum, micro phallus and undescended testicle. This result is compatible with the studies reporting that additional genital abnormalities coexisting with proximal hypospadias were more frequently observed in the presence of *46, XY* DSD (4,19,20). Different than the data in the literature, the most common diagnosis in proximal hypospadias cases was 5α-reductase deficiency, and PAIS. This result may have been caused by the high number of the cases diagnosed with 5α-reductase deficiency and PAIS in our study group.

Specific diagnosis in sex development disorders allows for providing the family and the patient with the optimum information with regards to long term expectations and results and giving support, timely treatment of necessary hormone replacements, determination of surgical options, fertility potentials and risk of cancer.

LIMITATIONS

The main limitation of our study is retrospective nature and that all etiologies could not be verified with molecular genetic diagnosis in all cases. Despite the limitations of this study, we believe that a consistent systematic DSD evaluation should be done for all cases with proximal hypospadias. Nonetheless, this gives an insight into how to diagnose *46XY* DSD, who may present at different ages and different clinical findings with different etiologies rearing.

CONCLUSION

Evaluating the results of the present study, it can be stated that proximal hypospadias is the most common referral clinic finding of *46, XY* DSD, and the risk of *46, XY* DSD increases with the intensifying degree of hypospadias and the presence of coexisting genital abnormalities. Considering diagnostic distribution of the cases with proximal hypospadias, it was detected that the majority of the cases formed 5α-reductase deficiency and PAIS and all of the cases with isolated hypospadias remained in this group. Although distal hypospadias is a common congenital anomaly, it was not seen in any of the cases diagnosed with *46, XY* DSD. Since early diagnosis and treatment may provide better cosmetic and functional results, all patients with proximal hypospadias should be followed in a multi-disciplinary center encompassing endocrinology, surgery/urology, psychiatry and genetics departments and should be evaluated for possibility of DSD.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: This study was approved by the local ethical committee (Sultangazi Haseki Training and Research Hospital, no: E-2020-57).

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