Increased Occurrence of Disorders of Sex Development, Prematurity and Intrauterine Growth Restriction in Children with Proximal Hypospadias Associated with Undescended Testes

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Abbreviations and Acronyms

DSD = sexual development disorder

PAIS = partial androgen insensitivity syndrome

UDT = undescended testis

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Purpose: Proximal hypospadias represents 20% of hypospadias cases, which are considered to have a higher incidence of associated urological, nonurological, developmental and sexual development disorders, and chromosomal anomalies. We compared associated anomalies in boys with proximal hypospadias and undescended testis with those in boys with proximal hypospadias and descended testes.

Materials and Methods: We reviewed the medical records of 69 boys who underwent 2-stage hypospadias repair for proximal hypospadias at a single institution during the 11-year period of 2001 to 2011. Collected data included demographics, birth history, associated urological and extra-urological anomalies, karyotype analysis and gonad palpability. Patients were divided into group 1—those with proximal hypospadias and undescended testis, and group 2—those with proximal hypospadias and descended testes. Statistical analysis was performed using the 2-tailed Fisher exact test.

Results: There were 17 patients (25%) in group 1 with a median age of 2.2 years and 52 in group 2 (75%) with a median age of 2 years. Children in group 1 had a higher incidence of XY nondysgenetic testicular sexual development disorder (8 vs 11, $p = 0.06$), premature birth (9 vs 10, $p = 0.01$) and intrauterine growth restriction (8 each) than children in group 2 ($p = 0.01$).

Conclusions: Prematurity and intrauterine growth restriction are significantly associated with proximal hypospadias and undescended testis. Also, due to the 28% incidence of an underlying sexual development disorder, male infants with proximal hypospadias should undergo multidisciplinary evaluation.

Key Words: genitalia, male; disorders of sex development; cryptorchidism; hypospadias; fetal growth restriction

Malformation of the external male genitalia occurs in approximately 1/300 live births.[1] Distal hypospadias is the most common form, often appearing as an isolated anomaly, while about 20% of cases are classified as proximal (scrotal and perineal). Cryptorchidism is also a commonly identified congenital anomaly, noted in approximately 0.8% of males at age 1 year.[2] The 2 anomalies develop simultaneously in 4% to 20% of cases.[3,4]

Proximal hypospadias, especially if associated with UDT, often requires urgent endocrine and urological evaluation to rule out a DSD. This clinical approach is based on studies showing a 27% incidence of DSD in a normal-appearing male with hypospadias and UDT, and a 53% to 100% incidence in patients with more severe forms of hypospadias and ambiguous genitalia.[5,6] In addition, a significant asso-

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ciation of hypospadias with poor intrauterine growth was described, suggesting that growth restriction probably occurs during early gestation and common environmental factors may cause each condition.[7]

We evaluated neonatal factors associated with the severe form of hypospadias. We also compared associated anomalies in children with proximal hypospadias and UDT to those in boys with proximal hypospadias and descended testes.

METHODS

We reviewed the medical records of all patients with proximal hypospadias who underwent operation at a single institution during the 11-year period of 2001 to 2011. This defect was diagnosed on physical examination by a consultant urologist based on the system proposed by Duckett. No patient was a suitable candidate for 1-stage hypospadias repair. Two-stage Bracka repair has been routinely performed in our practice for proximal hypospadias. We believe that Bracka staged repair is a versatile technique that is reproducible and provides excellent cosmesis.

The medical records were reviewed and entered in a computerized standard database, including information on gestational age, birth weight, investigations, diagnosis, and associated urological and nonurological anomalies. Patients were divided into group 1—those with proximal hypospadias and UDT, and group 2—those with proximal hypospadias and descended testes.

For study purposes infants were plotted on United Kingdom-WHO neonatal and infant close monitoring growth charts for boys (http://www.rcpch.ac.uk/growthcharts). Babies with a birth weight of below the 10th centile line were considered small for gestational age.

The diagnosis of 46XY nondysgenetic DSD involves the assessment of gonad palpability, karyotype analysis that includes fluorescence in situ hybridization and chromosome analysis of skin tissue samples, diagnostic imaging, eg pelvic ultrasound, cystoscopy and/or laparoscopy, steroid hormone analysis, β-human chorionic gonadotropin stimulation testing and androgen receptor binding studies, which have been replaced by androgen receptor mutation gene analysis. Statistical analysis was done using the 2-tailed Fisher exact test with $p < 0.05$ considered statistically significant.

RESULTS

We identified 69 boys with severe proximal hypospadias, including 17 (25%) with a median age of 2.2 years in group 1 and 52 (75%) with a median age of 2 years in group 2. The table lists the associated anomalies detected in patients who had hypospadias with UDT and in patients with isolated hypospadias.

Six and 11 of the 17 boys in group 1 had bilateral and unilateral UDT, respectively. Only 1 boy had an impalpable testis, which was identified in the inguinal canal on ultrasound. Eight children (47%) in group 1 had XY nondysgenetic testicular DSD, including PAIS in 7 and persistent müllerian duct syndrome in 1. At laparoscopy the boy with persistent müllerian duct syndrome was found to have a uterine remnant, fallopian tubes and the upper third of the vagina. Testicular biopsy revealed normal seminiferous tubules lined by Sertoli cells. XY nondysgenetic testicular DSD was identified in 11 children (21%) in group 2, including PAIS in 10 and 5α-reductase deficiency in 1 ($p = 0.06$). The latter was diagnosed by an increased serum testosterone-to-dihydrotestosterone ratio.

Associated abnormalities in groups 1 and 2

	No. Group 1 (%)	No. Group 2 (%)	p Value
Overall	17	52	
XY nondysgenetic testicular DSD	8 (47)	11 (21)	0.06
Prematurity	9 (53)	10 (19)	0.01
Intrauterine growth restriction	8 (47)	8 (15)	0.01
Chromosomal abnormalities	0	3 (6)	0.57
Renal anomalies	4 (24)	5 (10)	0.21

Overall, chromosomal anomalies were identified in only 3 patients (6%) in group 2, including 1 with 46XX DSD complete sex reversal and 2 with autosomal karyotype anomalies, that is a balanced translocation of 2q;15q and deletion of chromosome 13q in 1 each.

A higher rate of premature birth, defined as gestational age less than 37 weeks, was detected in group 1 vs 2 (9 patients or 53% vs 10 or 19%, $p = 0.01$). There was also a higher rate of intrauterine growth restriction in group 1 vs 2 (8 patients or 47% vs 8 or 15%, $p = 0.01$). Figures 1 and 2 show the relationship of hypospadias to intrauterine growth in the 2 groups. Of the children 24% and 10% in groups 1 and 2, respectively, had clinically significant renal tract anomalies, including a dysplastic or horseshoe kidney, duplex system and persistent utriculus ($p = 0.21$).

We also noted neurological anomalies in 6% of cases (craniosynostosis, tethered cord and lipoma of the cord), cardiac anomalies in 4% (Fallot tetralogy and a ventricular septal defect), ear, nose and throat anomalies in 4% (laryngomalacia and infraglottic cysts), abnormalities of the hands and feet in 4% (syndactyly and polydactyly), and anorectal malformation in 2%.

DISCUSSION

The prevalence of hypospadias is considered to be increasing worldwide but in Scotland there has been no reported significant increase (3.5/1,000 births).[1] Proximal hypospadias, which occurs in 20% of children with hypospadias, is characterized by proximal