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·*Review*·

Hypospadias: an update

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Abstract

Hypospadias is the most common congenital anomaly of the penis. The problem usually develops sporadically and without an obvious underlying cause. The ectopically positioned urethral meatus lies proximal to the normal site and on the ventral aspect of the penis, and in severe cases opens onto the scrotum or perineum. The foreskin on the ventral surface is deficient, while that on the dorsal surface is abundant, giving the appearance of a dorsal hood. Chordee is more common in severe cases. Cryptorchidism and inguinal hernia are the most common associated anomalies. The frequency of associated anomalies increases with the severity of hypospadias. For isolated anterior or middle hypospadias, laboratory studies are not usually necessary. Screening for urinary tract anomalies should be considered in patients with posterior hypospadias and in those with an anomaly of at least one additional organ system. The ideal age for surgical repair in a healthy child is between 6 and 12 months of age. Most cases can be repaired in a single operation and on an outpatient basis. Even patients with a less than perfect surgical result are usually able to enjoy a satisfactory sexual life. (*Asian J Androl 2007 Jan; 9: 16–22*)

Keywords: hypospadias; sporadic; cryptorchidism; inguinal hernia; renal anomaly; repair

1 Introduction

The word "hypospadias" is derived from the Greek words *hypo*, which means below, and *spadon*, which means rent or hole. Hypospadias is the most common congenital anomaly of the penis [1]. The condition is characterized by a urethral meatus that is ectopically located proximal to the normal location and on the ventral aspect of the penis. In severe cases, the urethral meatus opens onto the scrotum or perineum.

2 Embryology

At approximately 6 weeks of gestation, the genital tubercle develops anterior to the urogenital sinus. The urogenital membrane is flanked on each side by the outer genital swellings and the inner urethral folds [2]. Virilization of the male external genitalia occurs during the second month of gestation under the influence of testosterone synthesized by the fetal testes [2]. Placental human chorionic gonadotropin stimulates Leydig cells of the fetal testes to produce testosterone. Testosterone is converted to the more potent dihydrotestosterone by the enzyme 5α–reductase type II. For dihydrotestosterone to be effective, the hormone must bind to androgen receptors in the geni-

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tal tissues [2]. One of the first signs of virilization is an increase in the distance between the anus and the genital structures, followed by elongation of the phallus, formation of the penile urethra, and development of the prepuce [3]. The penile urethra forms as a result of the fusion of the medial edges of the endodermal urethral folds [3]. The fusion of endodermal urethral folds proceeds from proximal to distal and is usually completed by the end of the first trimester [4]. The ectodermal edges of the urethral folds then fuse over the urethra to form the prepuce [4]. It was formerly considered that the glandular urethra formed as an ectodermal ingrowth of tissue that invaginated through the glans to meet the proximal urethra [5]. However, recent evidence suggests that urothelium has the capability to differentiate into a stratified squamous epithelium, such that the entire male urethra can be formed by the fusion of the urethral folds [6]. Failure of fusion of the endodermal urethral folds leads to hypospadias.

3 Incidence

The incidence of hypospadias has been estimated to be 0.4 to 8.2 per 1 000 live male births [7, 8]. The wide variation is likely because of geographic, environmental or genetic differences and different methods in data collection [7, 9]. The condition is more common in Caucasians, least common in Hispanics, and intermediate among African-Americans [10]. There has been an overall increase in incidence of hypospadias both in Europe and North America [6, 7, 9]. Data from published studies in these jurisdictions suggest that the incidence of hypospadias doubled between the 1970s and the 1990s [6, 7, 9]. Data from the USA includes reports from the Metropolitan Atlanta Congenital Defects Program (MACDP) and the nationwide Birth Defects Monitoring Program (BDMP) [9]. The incidence of hypospadias measured by the BDMP increased from 20.2 per 10 000 live births in 1970 to 39.7 per 10 000 live births in 1993 [9]. The increase is unlikely to be attributable to increased access to medical care, improved recognition, or better reporting since the MACDP data showed that the rate of severe cases increased while the ratio of mild to severe cases decreased [9]. The rising rates might be a result of the increased incidence of premature infants with low birthweight, or to fetal exposure to progestins or to compounds with estrogenic or anti-androgenic activity [9]. No increase in the incidence of hypospadias has been noted in less-developed countries [6].

4 Etiology

The etiology is multifactorial. In the majority of cases the hypospadias develops as a sporadic problem and without an obvious underlying cause. In general, the more severe the hypospadias, the more likely an underlying cause can be identified [1]. Albers *et al*. [8] evaluated 33 patients with severe penoscrotal**,** scrotal, or perineal hypospadias with a range of diagnostic techniques that included clinical assessment, ultrasonography, karyotyping, endocrine evaluation, and molecular genetic analysis of the androgen receptor gene and the 5α-reductase gene. Notwithstanding such an extensive evaluation, the cause was determined in only 12 (36%) patients. Boehmer *et al*. [11] evaluated 63 unselected cases of severe hypospadias with clinical and molecular biological techniques and identified the cause in only 20 (32%) patients.

Defects in testosterone production by the testes and adrenal glands, failure of conversion of testosterone to dihydrotestosterone, deficient numbers of androgen receptors in the penis, or reduced binding of dihydrotestosterone to the androgen receptors could all result in hypospadias [8]. Several studies have shown subnormal testosterone response to human chorionic gonadotropin in some boys with hypospadias [12, 13]. Although the majority of boys with hypospadias have normal testosterone levels, this does not necessarily imply normal androgen production *in utero*.

Although the use of an oral contraceptive does not lead to hypospadias [14], maternal exposure during early pregnancy to other estrogenic compounds or to progestins might increase the risk of hypospadias [14, 15]. Environmental substances that contain estrogenic activity are common and include pesticides on fruits and vegetables, milk from lactating dairy cows, some plants, and pharmaceuticals. Klip *et al*. [15] conducted a survey of the 8 934 sons of a Dutch cohort of 16 284 women (response rate 67%) who were diagnosed with a fertility problem. Of the 205 boys born to mothers exposed to diethylstilbestrol during pregnancy, four had hypospadias. Only eight cases of hypospadias were reported in the remaining 8 729 children (odds ratio [OR]: 21.3; 95% confidence interval [CI]: 6.5–70.1). Pons *et al*. [16] analyzed the computerized files of 17 633 boys of mothers some of whom were exposed to diethylstilbestrol *in utero*. Three (1.2%) of the 240 boys with maternal exposure to diethylstilbestrol had hypospadias. Only 44

(0.5%) cases of hypospadias were found in the remaining 17 393 boys (OR: 4.99; 95% CI: 1.2–16.8). These findings confirm an increased risk of hypospadias in the sons of women exposed to diethylstilbestrol during pregnancy [16]. Several authors suggest that a maternal vegetarian diet, which contains higher amounts of phytoestrogens, might result in an increase in the incidence of hypospadias [17, 18]. Of 7 928 boys born to mothers who took part in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), 51 cases of hypospadias were identified [18]. The study showed a weak association between hypospadias and maternal consumption of a vegetarian diet high in soya products. Other authors did not find such as association [19, 20]. An association between maternal progestin intake and hypospadias has been noted in several studies [21, 22]. The National Birth Defects Prevention Study analyzed 502 boys diagnosed with severe hypospadias and 1286 control boys without hypospadias [21]. Forty-two case mothers (8.4%) and 31 control mothers (2.4%) reported progestin intake during the period from 4 weeks before conception through 14 weeks after conception (OR: 3.7; 95% CI: 2.3–6.0). There is evidence that activating transcription factor 3 (ATF3) responds to estrogenic or antiandrogenic activity and might play a role in the development of hypospadias [23, 24]. Liu *et al*. [25] examined the expression of ATF3 in penile skin tissue obtained from 28 children with hypospadias and in 20 normal tissue samples obtained during elective circumcision. Eighty-six percent of the samples from patients with hypospadias were immunohistochemi-cally positive for ATF3, compared with 13% of normal tissue samples [25]. Seventy-five percent of samples from patients with hypospadias were positive when tested by *in situ* hybridization, compared with 1% of circumcision samples. The study indicates that ATF3 is upregulated in the penile skin tissues of boys with hypospadias and suggests a role of ATF3 in the pathogenesis of hypospadias [25].

Maternal exposure to anti-epileptic drugs such as valproic acid might increase the risk of hypospadias [26]. Maternal exposure to xenoandrogens such as DDT (metabolite p,p'-DDE), vinclozolin, and diethylhexyl phthalate has been shown to cause hypospadias in animal studies [27, 28]. Data on human studies, however, are lacking. A higher incidence of hypospadias has been found in boys conceived by intra-cytoplasmic sperm injection (ISCI) or *in vitro* fertilization (IVF) [29, 30]. However, when controlled for other factors such as maternal age, parity, multiple or singleton birth, and paternal subfertility, the increased risk was not statistically significant [15, 31]. Several studies have shown that maternal smoking is not associated with an increased risk of hypospadias [14, 18].

Intrauterine growth retardation and low birthweight are risk factors for hypospadias [32, 33]. The risk increases with decreasing birthweight and is independent of gestational age [34]. Gatti *et al*. [33] found that hypospadias is 10 times more common in small-for-gestational-age infants compared with normal infants.

There is an increased incidence of hypospadias in both monozygotic and dizygotic twins [32]. Roberts *et al*. [35] noted that monozygotic male twins had an 8.5-fold increase in hypospadias, compared with singleton live male births. Fredell *et al*. [36] found that in 16 of 18 monozygotic pairs discordant for hypospadias, the twin with the lower birthweight had hypospadias. The mean difference in birthweight was 498 grams. The authors suggested that in the presence of two fetuses, there might be a relative placental insufficiency to one of the fetuses and less than adequate human chorionic gonadotropin to meet the demands of both pairs of male gonads [36]. The birthweight of a non-twin sibling without hypospadias is significantly higher than that of the proband with hypospadias [32].

Some authors suggest that advanced maternal age and primiparity are risk factors [6, 37]. Other authors did not find this association [38].

A high familial incidence of hypospadias is observed and a polygenic predisposition is likely [7, 39]. In a series of 1 314 cases of hypospadias reported by Leung *et al*. [39], 71 (5.4%) cases had at least one other affected relative. The risk of recurrence of hypospadias in a second male sibling is 12% to 14% [40]. About 7% to 9% of the fathers of boys with hypospadias also have hypospadias [2, 41]. If the father and the child are both affected, the risk of recurrence for a second sibling is increased to 26% [40, 42]. In general, the risk that a second male sibling will be born with hypospadias increases with the severity of hypospadias in the index child [1]. A dominant gene inheritance might be responsible for a small number of cases of hypospadias. Lowry *et al*. [43] reported two kindreds with familial hypospadias of different severity that affected members of at least two generations. Page [44] reported six instances of hypospadias in three or more generations and suggested a dominant Mendelian characteristic in these cases.

Frydman *et al*. [45] reported a large consanguineous Bedouin family that included eight members with various degrees of hypospadias. These authors postulated that an autosomal recessive inheritance might account for a subgroup of familial hypospadias.

Hypospadias has been found in various chromosomal aberrations, such as $4p^-$, $18q^-$, paracentric inversion of chromosome 14, and the Klinefelter syndromes [1, 46]. Hypospadias can be associated with genetic syndromes such as Smith-Lemli-Opitz, hypertelorism, hypospadias (BBB), hand-foot-genital, Reifenstein, Wolf-Hirschhorn, Denys-Drash, Silver-Russell, and G [1, 2, 46]. Hypospadias is a frequent finding with ambiguous genitalia of various causes such as hermaphroditism and mixed gonadal dysgenesis.

5 Clinical manifestations

The urethral meatus is ectopically located on the ventral aspect of the penis and proximal to the normal site, and might open onto the scrotum or perineum. The meatal position can be classified as anterior or distal (glandular, coronal, subcoronal), middle (midpenile), or posterior or proximal (posterior penile, penoscrotal, scrotal, perineal) [47]. The subcoronal position is the most common. Proximal cases are considered severe. Approximately 60% to 65% of cases are distal, 20% to 30% midpenile, and 10% to 15% proximal [47]. In severe cases, the scrotum might appear bifid [2]. The proximally displaced urethral meatus is often stenotic in appearance. Micropenis is uncommon except with severe cases associated with chordee [2].

Characteristically, the foreskin on the ventral surface is thin or absent while the foreskin on the dorsal surface is abundant and has the appearance of a dorsal hood [48]. In the rare megameatus intact prepuce (MIP) variant, the foreskin is normally developed and the urethral meatus has the appearance of a fish-mouth. In some cases, a blind-ending pit on the glans simulates a normal meatus and the only clue to hypospadias is a deficient ventral foreskin.

Chordee, derived from the Latin word *chorda*, which means string, refers to the ventral curvature of the penis. Chordee is caused by atrophy of the corpus spongiosum, fibrosis of the tunica albuginea and fascia over the tunica, tightness of the ventral skin and Buck's fascia, tethering of the penile shaft skin onto the underlying structures, or tethering of the urethral plate onto the corpora cavernosa [1, 47]. Chordee becomes more apparent and might only be noticeable with penile erection [1, 2]. The extent of chordee can be demonstrated by compression of the corpora cavernosa in the perineum, which causes the penile shaft to become engorged. With additional compression at the base of the penis, an erection can be elicited [7]. Chordee is more commonly associated with cases of proximal hypospadias. Chordee is best assessed intra-operatively with an artificial erection test (Gittes test).

The clinical presentation varies with severity of the disorder. Children with hypospadias and a narrow meatus may have a weak urinary stream that is deflected downwards and splayed. A normal stream might be present in those children with mild hypospadias who have a urethral meatus located on the glans. Affected children might not be able to void while standing. Uncorrected, erections might be painful in those children with chordee, and sexual intercourse might not be possible in severe cases. Fertility might be otherwise affected as the abnormal deflection of the ejaculate might preclude effective insemination.

6 Associated anomalies

Cryptorchidism and inguinal hernia are the most common anomalies associated with hypospadias [34, 49, 50]. Approximately 8% to 10% of boys with hypospadias have cryptorchidism and 9% to 15% have an associated inguinal hernia [49]. Clinicians should suspect the possibility of an intersex condition if a child with hypospadias also has cryptorchidism and one or both gonads are impalpable. Enlargement of the utriculus masculinus is present in approximately 11% of children with posterior hypospadias [6, 51]. Urinary tract anomalies such as ureteropelvic junction obstruction, vesicoureteric reflux, pelvic or horseshoe kidney, crossed renal ectopia, and renal agenesis occur in 1% and 5% of cases with isolated anterior and posterior hypospadias, respectively [6, 49]. When anomalies coexist in one, two, or three other organ systems, the incidence of an associated renal anomaly increases to 7%, 13% and 37%, respectively [49, 52]. There is a direct, almost linear relationship between the severity of hypospadias and the frequency of an associated anomaly [1]. Anterior and middle hypospadias are most often present as an isolated anomaly.

7 Diagnostic evaluation

Laboratory studies are not usually indicated for iso-

lated anterior or middle hypospadias. Screening for a urinary tract anomaly by renal ultrasonography should be considered in patients with posterior hypospadias and in those with an anomaly of at least one additional organ system. Karyotyping should be performed in patients with cryptorchidism or ambiguous genitalia [2, 8]. Other tests that should be considered include serum electrolytes, 17-hydroxyprogesterone, testosterone, luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin, ultrasonography of the abdomen, human chorionic gonadotropin stimulation tests, and molecular genetic analysis of the androgen receptor gene and the 5α reductase gene [8, 42]. The ordering of endocrine tests should be directed by the history, physical examination, and abnormal laboratory findings. In patients with associated micropenis, a pituitary evaluation followed by a trial of testosterone therapy should be performed [8].

8 Management

The goals of hypospadias surgery are to create a straight penis that is adequate for sexual intercourse, to reposition the urethral meatus to the penile tip to allow the patient to void while standing, to create a neourethra of adequate and uniform caliber, to construct a normal looking penis, and to accomplish the foregoing with as few complications as possible [6]. Surgical correction should also be considered in patients with a distal hypospadias and minimal deformity as the psychological benefit can be substantial [47]. The ideal age for surgical repair in a healthy child is approximately 6 to 12 months of age [53, 54]. The advantages of early surgery include easier after care, which includes better restraint for hygienic purposes and less likelihood of urinary catheter dislodgement, less separation anxiety, less need for analgesia, less postoperative emotional disturbance, and better parent-infant bonding [5, 53, 55]. After 6 months of age, the anesthetic risk is no greater than when the child is older [54]. Mureau *et al*. [56] found that boys who had surgical correction of hypospadias at an early age had fewer sexual inhibitions compared with boys who had surgical correction at a later age.

Penile size is usually not a limiting factor for early surgical correction [54]. If micropenis poses as a problem or if there is insufficient foreskin for repair, preoperative treatment with exogenous testosterone might improve the outcome [5, 54]. This can be achieved by the administration of testosterone enanthate, 20 to 25 mg intramuscularly, 3 and 6 weeks prior to surgery, or topical dihydrotestosterone cream applied daily for 1 month prior to surgery [6, 54]. For patients who still have an extremely small phallus at 6 months of age, a shift in the timing of repair to an older post-conceptional age may be necessary.

Many procedures have been designed for the repair of hypospadias and no single procedure is suitable for all cases. Most cases of hypospadias can be repaired in a single operation. The most common procedures include the meatal advancement-glanuloplasty (MAGPI), glans approximation procedure (GAP), and tubularization following incision of the urethral plate (TIP) [29, 57, 58]. A two-stage repair might be required for more severe forms of penoscrotal or perineal hypospadias [2, 59]. Complete excision of the chordee tissue is essential in patients with severe hypospadias and chordee. Suprapubic urinary diversion is not necessary when repairing hypospadias, no matter how severe the abnormality or how complex the repair is. Surgery should only be performed by a pediatric urologist or a surgeon with special and extensive expertise in hypospadias repair. In patients with hypospadias, circumcision is contraindicated as the foreskin might be needed for urethroplasty or to provide penile shaft skin coverage [2]. It is interesting to note that in MAGPI and TIP, the foreskin is not used in hypospadias repairs. With successful surgery, the appearance should be that of a normal circumcised penis and the cosmetic outcome is generally good.

Early complications of hypospadias repair include bleeding, hematoma, wound infection, wound dehiscence, necrosis of the shaft skin, urinary tract infection, and urinary retention [2, 60]. Late complications include urethrocutaneous fistula, meatal stenosis, recurrent or persistent chordee, urethral stricture, balanitis xerotica obliterans, urethrocele and urethral diverticulum [47, 61]. The rate of fistula formation is less than 10% for one-stage repairs in anterior hypospadias, and increases with the severity of the case. The rate of complications depends on the severity of the hypospadias, age at surgical correction, availability of adequate tissue for reconstruction, experience and skill of the surgeon, and whether there are previous failed attempts [60, 61]. Complications might be minimized by selecting the appropriate procedure, careful handling of tissues, optical magnification and the use of stents, and use of fine, absorbable material [55]. In experienced hands, complication rates for distal,

midshaft, and proximal repairs are < 5%, 5% to 10%, and 15%, respectively [55].

9 Prognosis

Children with hypospadias have normal onset of puberty [62]. Most patients with hypospadias have normal testicular and androgen end-organ functions [63]. Sexual function should be normal after successful hypospadias repair. Fertility should not be affected unless the patient has an associated anomaly such as cryptorchidism, a chromosomal abnormality, or a varicocele [1, 64]. Most patients, including those with a less than perfect result from hypospadias repair, are able to enjoy a satisfactory sexual life [64].

10 Conclusion

Hypospadias is the most common congenital anomaly of the penis. Identifiable causes implicate a deficiency in androgenic stimulation of fetal genital tissue, or conversely, exposure to excess estrogen or progestin containing compounds *in utero*. There is evidence that ATF3 responds to estrogenic or anti-androgenic activity and might play a role in the pathogenesis. A high familial incidence of hypospadias is observed and a polygenic predisposition is likely. In most cases, however, a cause cannot be identified. The ideal age for surgical repair in a healthy child is between 6 and 12 months of age. Most cases can be repaired in a single operation and on an outpatient basis. With modern surgical techniques and in the hands of an experienced pediatric urologist or surgeon, the functional and cosmetic results are usually very good.

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