INTRODUCTION

Hypospadias is the most common congenital anomaly of the penis, affecting 0.4–8.2 of 1000 live birth males (10- 15% of which are proximal hypospadias) ***(Giannantoni, 2011).***

Hypospadias is an association of three anatomical anomalies of the penis: an abnormal ventral opening of the urethral meatus, which can be located anywhere on the ventral aspect of the penis, an abnormal ventral curvature of the penis (chordee) and an abnormal distribution of the foreskin around the glans with the ventrally deficient hooded foreskin. The chordee is a common finding but not a constant one ***(Mouriquand et al., 1995).***

By meatal location hypospadias is classified as anterior (glanular and subcoronal), penile (distal penile and midshaft), and posterior (proximal penile, penoscrotal., scrotal., and perineal) accounting for 50%, 30%, and 20%, respectively ***(Montag et al., 2011).***

In the management of hypospadias preoperative assessment is of prime importance which should include measurement of the size of the phallus, glans cleft (flat, incomplete, or complete), location and size of the meatus (type of hypospadias and meatal stenosis or mega-meatus), urethral plate width (<1 cm or ≥1 cm), presence of chordee, penile torsion (clockwise, anticlockwise), shape of the scrotum

(normal., penoscrotal transposition), and associated anomalies e.g. cryptorchidism, inguinal hernia ***(Bhat, 2008)***.

The simultaneous occurrence of hypospadias with cryptorchidism increases the likelihood for disorders of sexual development (DSD) and should be further investigated by ultrasonography, hormonal profile, and karyotyping ***(Snodgrass, 2012).***

Timing of surgery is decided on the basis of anaesthesia's risk, penile size, and psychosocial development of the infant. The tolerance to anaesthesia is good at the age of 6 months; using microsurgical instruments and magnification, 6–18 months is the most suitable age for hypospadias repair. If the surgery is not performed during this age then the next window of surgery is preschool age (3-4 years) when the child starts cooperating with treatment ***(Manzoni et al., 2004).***

The goals in management of hypospadias repair are creating a straight penis, creating a urethra of adequate length and uniform caliber, reconstructing slit-like meatus at the tip of glans penis, symmetry in appearance of glans and penile shaft and projectile stream, these goals can be achieved by orthoplasty, urethroplasty, meatoplasty, glanuloplasty, scrotoplasty and skin cover ***(Bhat, 2008)***.

Minimal tissue trauma, minimal/pin-point use of cautery, and well-vascularized tension free repair of all layers with

epithelial inversion are the general principles of hypospadias repair. The goal of hypospadias repair is to build confidence in the child by creating a straight penis with a slit-like meatus at the tip of the glans and a urethra of uniform caliber and adequate length, reconstructing a symmetrical glans and penile shaft and achieving projectile stream and normal erection ***(Bhat, 2008)***. Most of the hypospadiologists favor the urinary diversion and postoperative dressing.

Complications after any surgical procedures are normal consequences within the standard acceptable percentage among surgeons. Complications are higher in hypospadias surgery as compared to other reconstructive operations. Urethrocutaneous fistula after hypospadias surgery repair is the most common complication and remains a frustrating problem for surgeons and other complications include meatal stenosis, neo-urethral stricture, urethral diverticulum, repair dehiscence and penile torsion ***(Latifoglu et al., 2000)*.**

While there is some variation in complication rates among various surgical techniques, generally the likelihood of problems is best predicted by severity of hypospadias corrected. Most complications require further surgery to correct, which typically is delayed for 6 months or longer to allow tissue reaction from earlier surgery to subside ***(Snodgrass, 2011)*.**

The term hypospadias cripple is used to describe the patient, who had undergone multiple, unsuccessful hypospadias repair attempts, with significant resultant penile deformity.

In this study we will investigate the demographic data and observe the outcome of different techniques used in repair of different types of hypospadias presented to our hospital through two years duration.

AIM OF THE STUDY

To present and analyze the postoperative outcome and complications of hypospadias repair and the factors influencing them at department of Urology Ain-shams university hospitals.

Chapter: (1)

PATHOGENESIS

The term hypospadias is derived from the Greek word "hypo" meaning under and "spadon" meaning rent or fissure ***(Duckett and Baskin, 1996; Zaontz and Packer, 1997).***

Hypospadias is a developmental anomaly that, in boys, is associated at birth with an ectopic opening of the urethral meatus on the ventral aspect of the glans or penis or in a scrotal or perineal position, abnormal distribution of the penile skin, lacking on the ventral aspect and abundant on the dorsal aspect; and sometimes ventral curvature, or chordee, of the penis ***(Mieusset and Soulie , 2005).***

Incidence of Hypospadias:

Hypospadias is the most common congenital anomaly of the penis, affecting 0.4–8.2 of 1000 live male babies (10- 15% of which are proximal hypospadias) ***(Giannantoni, 2011).***

In the 1800s both Bouisson and Rennes reported that hypospadias occurred in 1 of 300 males ***(Beck, 1917).*** Data from birth registries in the United States during the late 1960s demonstrated a similar incidence ***(Paulozzi et al., 1997).***

Prior to the 1970s data from several sources agreed the defect occurred in 1 of 300 boys; however, subsequent reports from both Europe and the US indicate a doubling of this rate to 1 in 150 ***(Snodgrass, 2011)*.**

There rising rates might be a result of increasing exposures to endocrine disrupting chemicals ***(Lund et al., 2009)***.

One of the main difficulties in reliably documenting changes in prevalence of hypospadias is the relatively common occurrence of more distal forms compared with severe forms, and the potential for incomplete, inaccurate, or inconsistent diagnosis and reporting of the more distal forms ***(Helen Dolk et al., 2004).***

So a review of the epidemiological data amassed to date on this issue clearly demonstrates that the bulk of the evidence refutes claims for an increase in hypospadias rates ***(Harry Fisch et al., 2010).***

The prevalence of hypospadias and their associated anomalies reported in literature varies greatly worldwide with large geographical differences observed ***(Abdelrahman et al., 2011; Mansoor Khan et al., Wu et al., 2000; Prat et al., 2012; Akin et al., 2011; Chung et al., 2012)***.

Etiology:

Hypospadias appears at the crossroads of genetic and environmental mechanisms ***(Kalfa et al., 2008)***. However there is a consistent conclusion that familial aggregation is best explained by genetic factors rather than environmental exposure ***(Schnack et al., 2008).***

A. Genetic etiologies:

1- Familial occurrence:

Many studies have demonstrated that hypospadias is a highly heritable condition, with overall heritability estimated to be 57 to 77%, this includes first, second, and third-degree relatives ***(Shih and Graham, 2014; Schnack et al., 2008).***

Interestingly, some studies have shown anterior (or distal/1stdegree) and middle (or 2nd-degree) hypospadias to occur more frequently in familial cases in comparison to posterior (or proximal/3rd-degree) hypospadias. On the other hand, low birth weight (a proxy for placental dysfunction) was more closely associated with proximal cases ***(Brouwers et al., 2010).***

2- Gene mutations:

A- The androgen receptor (AR) gene plays an important role in penile and urethral development and rarely AR gene

mutations have been found to be associated with hypospadias ***(Shih and Graham, 2014).***

However, murine studies indicating androgen receptor activity regulates Fibroblast growth factor 8, FGF10, and FGF2 involved in urethral development have led to screening for defects in these candidate genes in patients with hypospadias.

Among cases of nonsyndromic familial hypospadias variants have been found in FGF8 and FGFR2 not seen in normal controls ***(Alan et al., 2012).***

B- Partial androgen insensitivity syndrome, which is due to various AR gene mutations, varies in presentation, but typically involves perineoscrotal hypospadias and micropenis with normally functioning testes ***(Deeb et al., 2005).***

C- Estrogens also play a role in male development, with specific nuclear estrogen receptors, predominantly ER2, found in proximity to the androgen receptor. Variants of ER2 influence serum testosterone levels and have been described in patients with hypospadias ***(Beleza-Meireles et al., 2007).*** Further evidence implicating estrogen-related events in urethral mal-development was the finding that several estrogen-responsive genes are upregulated in hypospadias patients, including ACT3, Cyr61, CTGF, and CADD45β ***(Wang et al., 2007).***

D- Steroid 5-a reductase type 2 (SRD 5A2) is an enzyme that converts testosterone to DHT and plays a role in the formation of male external genitalia. SRD 5A2 is specifically expressed around the ventral part of the remodeling urethra during male genitourinary development. Pseudovaginal perineoscrotal hypospadias, due to a SRD 5A2 gene mutation, is an autosomal recessive condition that includes hypospadias, a bifid scrotum, and a blind vaginal pouch in a 46, XY individual, and during puberty results in the development of a male body habitus with phallic enlargement and semen production ***(Wang et al., 2007).***

E- The sex-determining region Y (SRY) gene is located on the Y chromosome and initiates male sexual differentiation by activating male-specific transcription factors, thus ultimately leading to testicular differentiation. However, research in this area has failed to show an association between hypospadias and SRY gene mutations ***(Wang et al., 2004).***

F- Gene mutations affecting the home box proteins (HOXA4, HOXB6), which are integral in the part of skin development that overlaps urethra formation, have also been found in patients with hypospadias ***(Beleza-Meireles et al., 2007).***

3- Polymorphisms:

Various single-nucleotide polymorphisms (SNPs) have also been associated with hypospadias, although many of these findings are only supported by a few studies. This isoform of 17 beta-hydroxysteroid dehydrogenase is expressed predominantly in the testis and catalyzes the conversion of androstenedione to testosterone. The HSD17B3 SNP involves a glycine-to-serine substitution, which leads to reduced levels of HSD17B3 mRNA expression in utero, and seems to be associated with hypospadias ***(Sata et al., 2010).***

Fibroblast growth factor 8 (FGF8) and fibroblast growth factor receptor 2 (FGFR2), both of which are involved in genital tubercle patterning, also have SNPs associated with hypospadias ***(Beleza-Meireles et al., 2007).***

B. Environmental etiologies

1- Medications/drug use:

Maternal usage of some medications has been associated with the development of hypospadias, such as valproic acid, which has gonadotropin- releasing hormone-agonist properties and thus, results in anti-androgenic effects ***(Jentink et al., 2010).***

Other maternal medications that have been reported as being associated with an increased risk of hypospadias (but require additional investigation at this point in time) include

iron ***(Brouwers et al., 2007)*** and anti-retroviral agents ***(Watts et al., 2007)*.**

In terms of illicit drugs, one study demonstrated a link between maternal cocaine usage and hypospadias ***(Battin et al., 1995)*.**

Most studies have not demonstrated a statistically significant association between maternal smoking and hypospadias ***(Van der Zanden et al., 2012)*,** but one study did report a significant association with paternal smoking exposure and increased hypospadias risk ***(Pierik et al., 2004)*.**

2- <u>Maternal factors:</u>

There are also maternal factors that are associated with an increased risk of hypospadias. One study found maternal obesity to be related to other structural birth defects, including hypospadias ***(Kallen, 2010)*.**

Additional maternal characteristics that have been implicated as possible risk factors for hypospadias include advanced maternal age, early menarche and primiparity. In terms of maternal conditions, pre-existing diabetes, thyroid disease, hepatitis B antigen carrier status, influenza, nausea and viral infection in the first trimester have all been suggested as possible contributors to an increased hypospadias risk, but such associations also need further investigation ***(Shih and Graham, 2014)*.**

Associated anomalies:

Approximately 9 to 15% of boys with hypospadias have an associated inguinal hernia and about 5–10% have cryptorchidism. In boys with more proximal hypospadias, cryptorchidism may occur as frequently as 50% and a persistent prostatic utricle may occur as frequently as 20% ***(Wilcox and Mouriquand, 2008).***

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 ***(Leung and Robson, 2007).***

Chapter: (2)

CLASSIFICATION

The meatal position can be classified as anterior or distal (glanular, coronal, subcoronal), middle (distal penile and midpenile), or posterior or proximal (posterior penile, penoscrotal, scrotal, perineal) ***(Leung and Robson, 2007)***.

In Smith's classification, the first degree locates the meatus from the corona to the distal shaft, the second degree from the distal shaft to the penoscrotal junction, and the third degree is from the penoscrotal junction to the perineum ***(Smith 1938)***. ***Schaefer and Erbes (l950)*** classified the location as glanular from the subcorona, penile from the corona to the penoscrotal junction, and perineal from there down. The system of ***Browne (1936)*** was more specific, with subcoronal, penile, midshaft, penoscrotal, scrotal and perineal varieties. ***Duckett (1966)*** classified hypospadias according to meatal location after release of curvature into anterior, middle and posterior hypospadias.

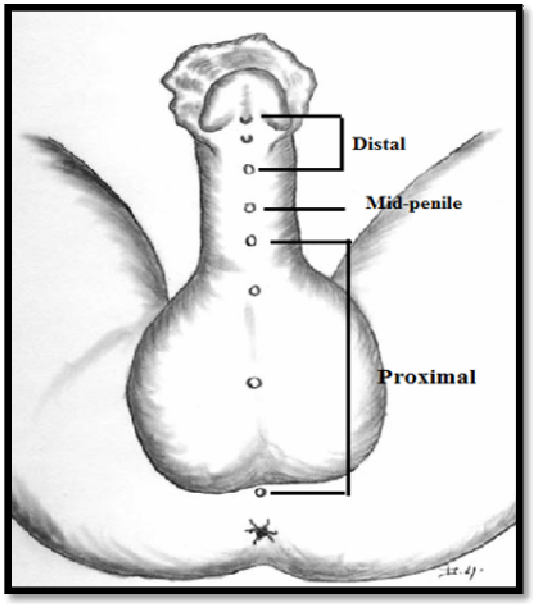

Figure (1): Hypospadias classification ***(Yachia, 2007)***

Present systems for categorizing hypospadias variants are based on the location of the external meatus with respect to specific penile elements and/or surrounding structures such as the scrotum or perineum ***(Orkiszewski, 2012).***

Difficulty in classification occurs when there are distally transposed scrotum, ventral curvature of the penis and/or hypoplasia of the tissues forming the ventral aspect of the penis ***(Orkiszewski, 2012).***

The Glans/Meatus/Shaft (GMS) hypospadias score is a standardized method for scoring the severity of the hypospadias complex, which includes, but is not limited to, meatal position. The criteria chosen were based on the anatomic features of