

Pathoembryology of Hypospadias and Chordee

Abstract

Hypospadias is one of the most common congenital anomalies in childhood. It refers to displacement of the external urethral meatus toward the undersurface of penis, the scrotum or the perineum. Congenital abnormal curvature of the penis is termed as "chordee" and it may be dorsal or ventral and of varying degree. Genetic as well as environmental antiandrogenic and estrogenic factors are blamed for the etiology of congenital penile malformations. Morphological patterns of prepuce and of dartos tissue are described. In some instances, preoperative treatment with testosterone is indicated. Different surgeries are mentioned for the repair of hypospadias, penile torsion and chordee.

Keywords: Hypospadias; Chordee; Etiologies; Prepuce; Dartos tissue; Preoperative hormonal therapy; Surgical repair

Review Article

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Heshmat SW Haroun*

Professor of Anatomy and Embryology, Cairo University, Egypt

***Corresponding author:** Heshmat SW Haroun, Professor of Anatomy and Embryology, Faculty of Medicine, Cairo University, Egypt, Email: heshmatsabet@gmail.com; heshmat.haroun@kasralainy.edu.eg.com; heshmat.haroun@scholar.cu.edu.eg

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Abbreviations: AMH: Anti-Mullerian Hormone; AR: Androgen Receptors; ATF3: Activating Transcription Factor 3; CPAs: Congenital Penile Anomalies; CWH: Chordee Without Hypospadias; EDCs: Endocrine Disrupting Chemicals; KFS: Klinefelter Syndrome; LUTS: Lower Urinary Tract Symptoms; MAGPI: Meatal Advancement and Glanuloplasty Incorporated; SMR: Split Median Raphe; TEV: Talipes Equinovarus; UTIs: Urinary Tract Infections

Introduction

Hypospadias is an abnormal development of the penile urethra that results in displacement of the external urethral meatus from its normal site on the tip of glans penis to anywhere along the ventrum of the penile shaft, in the scrotum, or in the perineum. In severe cases, it is associated with penile chordee. Hypospadias is considered as the second most common birth defect in humans as it affects one in every 250 children [1]. The site of hypospadias may be distal, mid-shaft, or proximal shaft with an incidence of 94%, 4%, and 1% respectively [2]. The megameatus - intact prepuce variant of hypospadias is a congenital anomaly that is featured by a broad spatulated glans penis, an intact prepuce, lack of history of bleeding at the time of circumcision, and a large patulous external urethral meatus that lies on a deep subglandular groove [3,4]. Elastasonography has showed markedly altered anatomy in hypospadiac penis in the form of stiffer and less elastic corpus spongiosum (and penis) as well as less developed corpora cavernosa [5]. Intrauterine diagnostic measurement of penile width is a convenient method to diagnose micropenis, but alone cannot give a clue to some other penile abnormalities including chordee and hypospadias [6] (Figure 1).

Pathoembryology of Hypospadias and Chordee

Hypospadias has been recently increased during the last three decades and its etiology remains unclear although genetic, hormonal, and environmental factors appear to be the main inducers [7,8]. Descent of the testis is a prerequisite for normal development of the external genitalia and cryptorchidism is commonly associated with hypospadias [9]. In isolated cases of

microphallus or hypospadias, decreased values of serum anti-Mullerian hormone (AMH) is in favor of testicular dysfunction and external genitalia anomalies in human fetuses, newborns, and prepubertal children [10]. The presence of androgen receptors (AR) in the developing male genitalia is essential for their proper development and in addition estrogen receptors have been recently demonstrated; their genetic polymorphism might influence the incidence of hypospadias [11]. The activating transcription factor 3 (ATF3) gene is estrogen-responsive and its stimulation at an early stage in estrogen-exposed male fetuses is more likely to lead to penile urethral anomalies [12]. Vinclozoline, as a fungicidal drug, when given to pregnant rats it induced hypospadias in male and longer urethra in female genital tubercles of the offsprings [13].

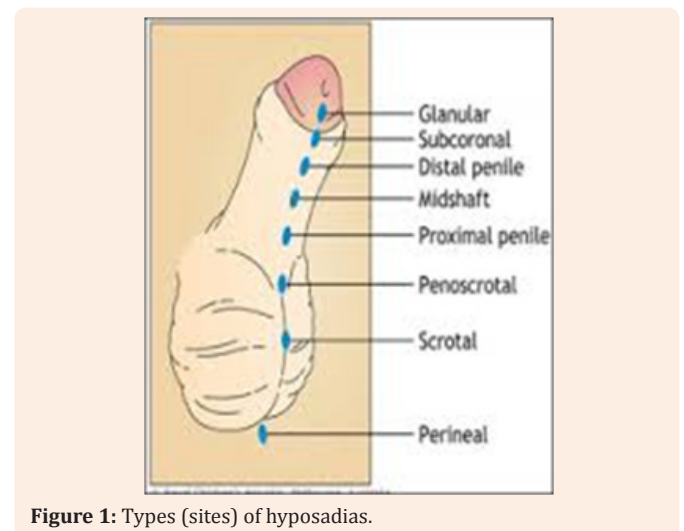


Figure 1: Types (sites) of hypospadias.

Both genetic conditions and environmental factors, such as antiandrogenic and estrogenic endocrine disrupting chemicals (EDCs), are suspected to cause congenital penile anomalies (CPAs). Prenatal disruption of androgen receptor (AR) at different developmental stages in the mouse genital tubercle results in

hypospadias and chordee, whereas earlier disruptions cause ambiguous genitalia and later disruptions cause micropenis [14]. AR expression is found to be decreased in penile preputial skin of patients with congenital hypospadias and simple chordee, when compared to control prepuce [15].

Klinefelter syndrome (KFS), is the most common disorder of the sex chromosomes, affecting 1/1000 male births. It presents with underdeveloped secondary sexual characteristics, infertility, and increased urinary excretion of gonadotropin. In males with a 47XXY karyotype, hypospadias and concomitant chordee could be identified. Klinefelter syndrome is also reported to be associated with perineal hypospadias, severe ventral chordee and complete penoscrotal transposition [16].

In a mouse model, the genital tubercle showed two epithelial folds that approached each other to complete the urethral tube (canal); of which the lining cells were of vesical origin while the surface cells were of skin origin [17]. Incomplete fusion of the embryonic urethral folds and failure of canalization of the glandular urethra have been believed for a long time to be the only explanation for the occurrence of hypospadias in man [18-20]. Recently, this urethral anomaly has been attributed to defective development of a complex of fascial and vascular tissues proximal to the urethral orifice. This tissue - complex normally proliferates to form the ventrum of the penile shaft and to push the urethral orifice distally. Furthermore, insufficient or disorganized growth of the complex may lead to penile chordee [21].

Split median raphe (SMR) of the penis is thought to be due to defective fusion of ectodermal tissue in the region of the urethra and scrotum area or to defective growth of the perineal mesoderm around the urethra during gestation. SMR may be an isolated malformation or commonly associated with other major penile congenital defects as epispadias, hypospadias, penile torsion, bifid scrotum, or chordee [22].

Congenital fistula of the penile urethra is a rare anomaly [23-25]. It is hypothesized that congenital urethral fistula and congenital chordee without hypospadias are due to defective development of the urethral plate. It is also added that deficiency of a testicular evocator prior to complete development of the urethra is the only possible explanation for the etiology of hypospadias [26]. Congenital penile urethrocutaneous fistula is described as an unusual anomaly in children who present with an abnormal opening on the ventrum of the penis with a normal foreskin and an absence of chordee and hypospadias [27].

Morphology of Hypospadiac Prepuce

In hypospadiac boys, the prepuces are classified into morphological types: "monk's hood", "cobra eyes", "normal intact", "flat", "v-shaped", and "collar-scarf" with the "cobra eyes" type predominating, the first two types having the most favorable vascular pattern for repair, and the v- and flat- types having the most unfavorable vascular pattern [28]. In an investigation on Taiwan elementary schoolboys, prepuces were categorized into: normal prepuce, prepuce with adhesions, partial phimosis, phimosis, and circumcised [29].

The arterial supply of hypospadiac prepuce differs from that of normal prepuce. Different patterns of normal preputial arteries are described as one artery-predominant (42%), two arteries-predominant (25%), H-arching (12%), and network of arteries (21%) while in hypospadiac prepuces there is prevalence (50%) of the network pattern [30]. It is emphasized on the significance of knowledge of the vascular anatomy of the hypospadiac prepuce for better surgical repair. Furthermore, the hypospadiac prepuce is mostly hypoinnervated when compared to the normal prepuce, and this may lead to poor postoperative healing [31].

Preoperative Hormonal Therapy

Preoperative hormonal therapy is currently used before hypospadias surgery. There is a great dilemma in the literature regarding the hormone of choice, time of its use before surgery, appropriate dose, and route of administration. The benefit of hormonal therapy toward penile improvement and better surgical results is still not well-defined [32,33]. Preoperative oral testosterone undecanoate is reported to effectively improve the temporary penile growth, significantly increase the penile length and diameter, and decrease the surgical complications in children with microphallic hypospadias [34]. Parenteral testosterone before hypospadias repair is also beneficial in decreasing surgical complication rates [35].

Surgical Repair

Hypospadias is usually corrected in childhood. Mild untreated hypospadias had fewer adverse outcomes in adults than severe hypospadias [36]. Circumcision is one of the most commonly performed surgeries during childhood. Proper examination of boys, by primary care physicians prior to circumcision, provides early detection of penile anomalies which can be corrected at the same session [37,38]. On the other hand, repair of hypospadias in a child likely increases the future risk of urethral stricture, recurrent urinary tract infections (UTIs), and subsequent lower urinary tract symptoms (LUTS) but with improvement of patient's satisfaction with cosmesis when compared to nonsurgical management [39,40]. In glandular and coronal hypospadias, meatal advancement and glanuloplasty incorporated (MAGPI) repair provides excellent functional and cosmetic outcomes with minimal complications, and it can safely be performed as a day-case procedure [41]. Future of hypospadiology is bright with upcoming newer modalities like laser shouldering, robotics, and tissue engineering [42].

Penile Curvature, Torsion and Chordee

Congenital penile curvature and chordee are rare malformations most frequently associated with hypospadias. Varying degrees of dorsal or ventral penile curvature are observed with an orthotopic meatus and the condition becomes evident after puberty when curvature becomes more apparent with erection [43]. Penile torsion is a congenital malformation that results in a rotational deformity of the penile shaft [44]. Proximal severe forms of hypospadias are particularly accompanied by congenital penile curvature (chordee) [45]. Correction of coexistent penile torsion and chordee without hypospadias is achieved by mobilization

of the urethra and corpus spongiosum [46]. Cases of chordee without hypospadias (CWH) are effectively corrected by plication of the tunica albuginea in both prepubertal and postpubertal periods and also in case of recurrence [47,48]. Meticulous tissue handling and urethroplasty are needed for satisfactory results in correction of CWH [49]. Correction of penile torsion was also mentioned to be possible through penile de-gloving, mobilization of urethral plate and spongiosum, mobilization of proximal urethra, and mobilization of urethral plate/hypoplastic urethra with spongiosum into the glans penis [50]. Bulbar elongation and anastomotic meatoplasty procedure gave an excellent cosmetic and functional outcome in a case of dorsal chordee [51]. Urethral mobilisation alone cannot completely correct moderate and severe penile torsion but it only decreases the angle of torsion. Periosteal anchoring of the tunica albuginea, in addition to urethral mobilization, might be the most reliable procedure for the complete correction of penile torsion [52].

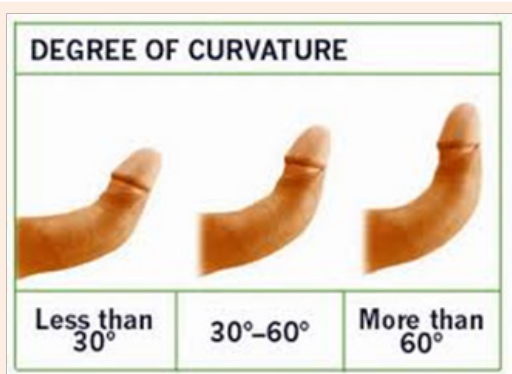


Figure 2: Dorsal chordee.

Acknowledgment

None.

Conflict of Interest

None.

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Congenital penile anomalies (hypospadias, chordee and buried penis) are associated with structural anomalies in the dartos tissue. Resection of dartos tissue usually straightens the penis in patients with chordee and buried penis, suggesting a common pathophysiology related to dartos tissue. Dartos tissue is reported to have three patterns: normal pattern I consisting of parallel smooth muscle fibers within the subcutaneous tissue, pattern II of poorly developed smooth muscle fibers, and pattern III of widely dispersed smooth muscle fibers within the subcutaneous tissue [53].

In a study on infants with talipes equinovarus (TEV) at birth, few of them with "isolated TEV" showed associated malformations that had not been identified by imaging during pregnancy in the form of hip dislocation, bilateral post-axial polydactyly of the feet, penile chordee, and hypospadias [54] (Figure 2 & 3).



Figure 3: Ventral chordee with hypospadias.

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