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What is the pathogenesis of proximal hypospadias?

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ABSTRACT

Objective: To report the information concerning the pathogenesis of proximal hypospadias and causes of curvature associated with it.

Material and methods: From January 2009 to December 2015, 74 patients underwent repair of proximal hypospadias. In 70 patients we performed a systematic biopsies in the lateral areas of the urethral plate, as well as under this plate. The study of the histological structure of these areas was performed using routine staining with hematoxylin and eosin, and the Masson's trichrome which color the collagen fibers in blue and monoclonal antibody against alpha-smooth muscle actin.

Results: This prospective study shows that the fibrotic tissue abnormally present on the ventral side of the penis consists of a mixture of fibrous connective tissue, nerve nets, short vessels, and smooth muscle fibers. In contrast to the scrotal dartos, penile dartos fascia does not contain smooth muscle fibers. Therefore, these fibers may come from a blood vessel or spongy tissue which existed during neonatal period in the distal part of the penis before disappearing. In addition, in 13 cases, the presence downstream of the urethral meatus, of a bifurcation of corpus spongiosum into two branches supposes that the corpus spongiosum is form by fusion around the urethra of two mesenchymal bodies. The arterial supply of this purely masculine formation originates from a new vascularization and it is probably, developed under secretion of androgens (angiogenic substances in target tissues).

Conclusion: These findings allow us to suggest that the proximal hypospadias is due to avascular necrosis of the distal part ie. poorly vascularized part of the corpus spongiosum.

Keywords: Etiology of hypospadias; chordee; curvature; hypospadias; pathogenesis of chordee; pathogenesis of hypospadias.

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Introduction

The term hypospadias is a Greek word composed of two words: Hypo (νπο) which means under and spathe (σπαδη) which means sword. It represents the most common urogenital malformations in boys and it is characterized by ectopia of urethral meatus. This meatus is located on the ventral side of the penis or on the scrotal area.

The proximal forms represent approximately one third of cases of this malformation. These forms are very often associated with a curvature.[1] Thus, the treatment of proximal hypospadias should include two surgical stages: correction of the curvature and urethroplasty. The choice of the surgical technique of urethroplasty depends on the method of curvature correction.

The mechanism of formation of the curvature remains unknown and its correction has evolved throughout time thanks to a better understanding of its causes. In the past, the urethral plate was systematically resected in proximal hypospadias repair since the work published by Mettauer[2] which incriminated the urethral plate in the formation of the chordee. However, in 1970s, King[3] and Marshall

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et al.[4] showed that it was unnecessary to transect the urethral plate to correct the curvature. Koyanagi et al.[5] then Mollard et al.[6] proposed the release of curvature by mobilizing the urethral plate with resection of the underlying fibrous tissue. Recently, it has been shown that there are cases where it is difficult to preserve the urethral plate in the correction of the curvature, especially when the initial curvature is >90.[1]

The aim of the present study is to report the information concerning the causes of curvature associated with proximal hypospadias and to try to explain the pathogenesis of proximal hypospadias based on anatomical and histological findings encountered in patients treated for this urogenital malformation.

Material and methods

Ethics Committee Approval obtained for the study conforms to the World Medical Association Declaration of Helsinki (June 1964) and subsequent amendments and the investigations were carried out to a high ethical standard. However, in our country there is not a formal and documented ethical approval form which should be obtained from an appropriately constituted research ethics committee for all studies involving human beings.

Between January 2009, and December 2015, 74 patients underwent repair of proximal hypospadias associated with chordee. In 70 cases, the biopsies were performed in the lateral areas, as well as under the urethral plate. The study of the histological structure of these areas was performed by routine staining with hematoxylin and eosin (H&E), the Masson's trichrome which colorthe collagen fibers in blue (Figure 1a) and monoclonal antibody against alpha-smooth muscle actin. The use of monoclonal antibody against alpha-smooth muscle actin gives the smooth muscle fibers a brown color (Figure 1b).

We also used lateral photographs taken of each patient during successive saline erection tests to measure with precision the degree of correction obtained after each stage. Saline erection tests were performed firstly at the start of the operation, then after release of the skin and dartos fascia (2nd test), after possible mobilization of the urethral plate and resection of the underlying fibrous tissue (3rd test), and the last test at the end of the operation.[7]

The position of urethral meatus before release of the curvature is showed in Table 1. Testosterone was used before surgery for 5 patients (7.14% of the cases) who have a penis length <2.5 cm and/or diameter <1 cm. A 2 mg/kg dose of testosterone was given to the patients through intramuscular injection, sometimes two injections were given on 21 day-interval to increase the size of the penis. The age of the patients who underwent the surgery ranged from 9 to 54 months (mean 28.73 months). The median follow-up was 39 months (range, 1-84 months).

The surgical correction always started by an evaluation of the initial curvature of the penis with an artificial erection test. A traction suture was placed through the glans, and an incision was made 2 mm proximal to the hypospadiac meatus and extended distally by 2 parallel incisions in the skin and the glans (U-shaped incision). This incision isolated a sufficiently wide urethral plate (8-10 mm). Then, the skin and the dartos fascia

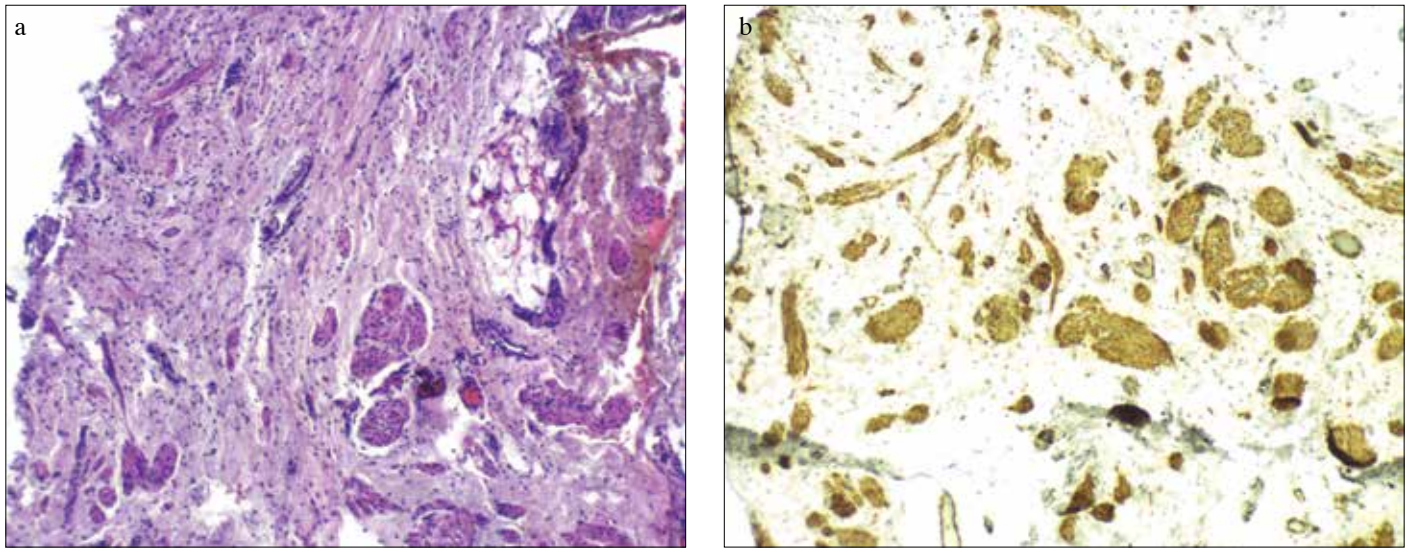

Figure 1. a, b. Biopsy made on the ventral side of the penis (in the lateral areas of the urethral plate) shows: (a) Fibrotic tissue with smooth muscle fibers (X100). (b) Use of monoclonal antibody against alpha-smooth muscle actin revealed the presence of the smooth muscle fibers (smooth muscle fibers in brown)

were dissected from the shaft. This dissection must be extended to the perineal area.[8] The correction obtained was evaluated with a second artificial saline test. If this test demonstrated persistent penile curvature the urethral plate was lifted up from the corpora cavernosa by a fine scissors slipped between the urethral plate and corpora cavernosa. All the fibrous tissue would then be resected. A new artificial test was made, the angulations ≤20° was acceptable. However, if a significant degree of chordee remained, we performed a dorsal plication of the tunica albuginea by excision of a diamond-shaped tissue at the point of the maximum dorsal bend.[7]

Sometimes, the urethral plate was resected and the urethroplsty was made by tubularized island flap or in two stages.

Statistical analysis

A descriptive study of 70 patients with univariate statistical analysis.

Results

The biopsies clearly showed that the dartos fascia in the ventral side of the penis was replaced by fibrosis tissue. This tissue consists of a mixture of fibrous connective tissue, nerve nets, short vessels, and smooth muscle fibers (Figure 1). The use of monoclonal antibody against alpha-smooth muscle actin revealed the presence of smooth muscle fibers within the fibrous tissue in 41 patients (58.6% of cases).

The analysis of the lateral photographs taken at the successive saline erection tests clearly demonstrated that the curvature of the penis was present in all cases. This curvature was ≤45° in 10 (14.28% of cases), 45-90° in 36 (51.5%) and ≥90° in 24 patients (34.28%) and the release of skin and dartos fascia provided a significant correction of the chordee, ranging from 20° to 100°. Dorsal plication of the tunica albuginea by resection of a diamond-shaped tissue at the dorsally bend was performed as a straightening procedure for the penis in 6 patients (8.57%), and the urethral plate was resected in 12 cases (17.14%).

Table 1. The position of urethral meatus before release of the curvature

Initial position of urethral meatus	Number	The length of pellucid part of the urethra
Subcoronal	2	26 mm and 13 mm
Midshaft	17	1-15 mm
Proximal penile	18	1-17 mm
Penoscrotal Junction	19	1-7 mm
Scrotal or perineal	14	1-5 mm

The onlay island flap urethroplasty was performed for 53 patients (75.71% of cases) and the urethral plate was tubularized for five patients (7.14% of cases). When the urethral plate had been resected, urethroplasty was performed with a tubularized island flap in 8 patients (11.43%) and in two stages in 4 patients (5.71%).

All patients underwent urinary diversion through a feeding tube (6 or 8F) which remained *in situ* for 2-8 days and antibiotic prophylaxis maintained for 5 days.

Discussion

The essential factor responsible for the curvature associated with proximal hypopsadias is the fibrotic tissue present on the ventral side of the penis. However, when the initial curvature is more than 90 degrees, a short urethral plate becomes the main cause of this curvature.[1]

For more than 20 years we have been using a dorsal plication technique by excision of a diamond-shaped tissue at the point of the maximum bend dorsally after complete separation of the dorsal neurovascular bundle from the corpus cavernosum. Dorsal plication seems to be more physiologic than others and allows preservation of the urethral plaque, even in cases with significant curvatures. However, it is still a difficult surgical manipulation which requires experienced hands and especially, and its usefulness has been questioned.[9] A significant number of adults and adolescents under our surveillance had benefited during their young age from an onlay island flap urethroplasty with or without mobilization of urethral plate and dorsal plication later on reported the presence of curvature during erection.[1] Our attitude towards proximal hypospadias associated with curvature totally changed two years ago. The correction of the curvature should be a priority and do not hesitate to transect the urethral plate, if the release of the curvature requires it and we do not practice the dorsal plication anymore. When the urethral plate was resected, the urethroplasty was created using tubularized island flap[10] or by Koyanagi-Hayashi's procedure[11,12] or in two stages. However, when the preservation of urethral plate is possible; this plate can be used as a solid template for urethroplasty by onlay island flap.[6] It can be also tubularized[5] or recently used as a tubularizedi plate according to Snodgrass and Bush.[13]

Hypospadias is due to defect of distal corpus spongiosum and urethra. However, its pathogenesis remains unknown. Several causes of hypospadias have been suggested:

Genetic etiology: All abnormalities of genes which regulate the secretion of androgens (AR gene, SRD5A gene, HSD17B3 gene, FKBP4 gene, MAMLD1, CYP17A1 gene, HSD3B2

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gene) and fibroblast growth factor genes (FGF8 gene, FGF10 gene, FGF2)[14] can be etiological factors of severe forms of hypospdias.

Hormonal etiology of maternal origin: especially progestin, estrogens[15] corticosteroids.

Toxic etiology: the substances which interfere with the endocrine system of the fetus such as dioxins, organochlorine pesticides,[16] and phytoestrogens in vegetarian women.[17]

The pathogenesis of hypospadias remains unknown. However, several factors lead us to believe that the proximal hypospadias and curvature are due to avascular necrosis of the distal poorly vascularized part of the corpus spongiosum, immediately after its separation from the rest of mesenchymal tissue (between 4 to 5th months of pregnancy). This necrosis is probably the cause of the disorderly development of the single artery of this body (during the transition from a state of two arteries to only one):

The fibrotic tissue abnormally presents itself on both sides of the urethral plate in the proximal hypospadias with curvature, a rich tissue in nerve fibers, short blood vessels, and smooth muscle fibers. In contrast to the scrotal dartos fascia, penile dartos fascia does not contain smooth muscle fibers. Therefore, these fibers can come from a blood vessel or spongy tissue which existed during neonatal period in the distal part of the penis before its disappearance.

Virilization of the external genitalia occurs mediated by D.H.T. (dihydrotestosterone) between the 12th and 14th weeks of gestation: The genital tubercle elongates considerably, the labioscrotal folds merge in the midline to form the scrotum, and the urethral gutter is closed from behind by a phenomenon of endodermal tubulisation. After the 14th week, the fusion of the labioscrotal folds cannot occur even under intense androgenic stimulation. Although the phallic growth can be induced, the penile urethra completely formed at the 14th weeks has a blind end and reaches the base of the glans, while the balanic part of the urethra is formed secondarily by ectodermal intussusceptions in the 4th month. At the same time that the penile urethra forms, the mesenchymal tissue which surrounds it becomes denser and forms the roughing of the corpus spongiosum, but the transformation of the mesenchymal tissue to erectile tissue occurs only secondarily, between the 4th and 5th months of pregnancy. However, in some cases of hypospadias, the presence downstream of the urethral meatus, of a bifurcation of corpus spongiosum into two branches, more visible in pubertal children (Figure 2) suggests that the corpus spongiosum is formed by fusion of two mesenchymal bodies around the urethra. In addition, the final arterial system is formed before the 9th week of gestation; this assumes that the arterial supply of this purely masculine formation (corpus spongiosum) originates from a new vascularization; probably developed under the impact of secretions of androgens (angiogenic substances in target tissues).

Figure 2. Bifurcation of the corpus spongiform into two branches in a child of 13 who had an anterior hypospadias

In case of incomplete and chronic ischemia of an organ tissue or infarct (ischemic necrosis of an area in solid organ by obstruction of a terminal artery), the tissue of this area is gradually transformed into fibrosis with the retraction of the affected area. In addition, French researchers have discovered the element responsible for the fibrosis namely pathological fibroblasts which induce overproduction of scar tissue. These researchers showed that these cells which overproduce collagens are characterized by the expression on their surfaces of membrane protein, known as ADAM.[18] This work is very interesting, it permits to understand wound healing in the fetus. This type of fibroblasts, which do not normally exist in adults are usually present in fetuses, which assumes that the cicatrization in a fetus is always complicated by fibrosis.

In summary, the curvature associated with proximal hypospadias is due to the fibrotic tissue abnormally present on the ventral side of the penis (in the lateral areas and behind of the urethral plate, as well as under the urethral plate). This tissue consists of a mixture of fibrous connective tissue, nerve nets, short vessels, and smooth muscle fibers. However, the penile dartos fascia does not contains smooth muscle fibers.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

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References

1. Acimi S, Acimi MA. Can We Preserve the Urethral Plate in Proximal Hypospadias Repair? Ann Plast Surg 2017;79:68-72.
2. Mettauer JP. Practical observations in those malformations of the male urethra and penis, termed hypospadias and epispadias, with an anomalous case. Am J Med Sci 1842;4:43-58. [CrossRef]
3. King LR. Hypospadias-a one-stage repair without skin graft based on a new principle chordee is sometimes produced by the skin alone. J Urol 1970;103:660-2. [CrossRef]
4. Marshall M Jr, Beh WP, Johnson SH III, Price SE, Barnhouse DH. Etiologic considerations in penoscrotal hypospadias repair. J Urol 1978;120:229-31. [CrossRef]
5. Koyanagi T, Matsuno T, Nonomura K, Sakakibara N. Complete repair of severe penoscrotal hypospadias in 1 stage: experience with urethral mobilization-wing flap-flipping urethroplasty and "glanulomeatoplasty". J Urol 1983;130:1150-3. [CrossRef]
6. Mollard P, Mouriquand P, Felfela T. Nouvelle technique de traitement des hypospades avec coudure par utilisation du lambeau en onlay. Prog Urol 1991;1:305-11.
7. Acimi S. Intérêt de la mobilisation de la plaque urétrale dans la libération de la courbure qui accompagne les formes postérieures d'hypospadias. Prog Urol 2005;15:59-62.
8. Acimi S Proximal hypospadias: effect of urethral plate mobilization on release of chordee. Urology 2012;80:894-8. [CrossRef]
9. Acimi S. Commentary: Management of High-Grade Penile Curvature Associated with Hypospadias in Children. Front Pediatr 2017;5:261. [CrossRef]
10. Duckett JW. Transverse preputial island flap technique for repair of severe hypospadias. Urol Clin North Am 1980;7:423-30.
11. Koyanagi T, Nonomura K, Kakizaki H, Takeuchi H, Yamashita T. Experience with one-stage repair of severe proximal hypospadias: Operative technique and results. Eur Urol 1993;24:106-10. [CrossRef]
12. Hayashi Y, Kojima Y, Mizuno K Nakane A, Kohli K. The modified Koyanagi repair for severe proximal hypospadias. BJU Int 2001;87:235-8. [CrossRef]
13. Snodgrass W, Bush N. Tubularized incised plate proximal hypospadias repair: continued evolution and extended applications. J Pediatr Urol 2011;7:2-9. [CrossRef]
14. Beleza-Meireles A, Lundberg F, Lagerstedt K, Zhou X, Omrani D, Frisén L, et al. FGFR2, FGF8, FGF10 and BMP7 as candidate genes for hypospadias. Eur J Hum Genet 2007;15:405-10. [CrossRef]
15. Mieusset R. Hypospadias. Epidemiologie des hypospadias. 1rst d Ed. Sauramps Médical. 2003. p. 24-244.
16. Carmichael SL, Ma C, Werler MM, Olney RS, Shaw GM. Maternal corticosteroid use and hypospadias. J Pediatr 2009;155:39-44. [CrossRef]
17. North K, Golding J. A maternal vegetarian diet in pregnancy is associated with hypospadias. The ALSPAC Study Team. Avon longitudinal study of pregnacy and childhood. BJU Int 2000;85:107-13. [CrossRef]
18. Dulauroy S, Di Carlo SE, Langa F, Eberl G, Peduto L. Lineage tracing and genetic ablation of ADAM12(+) perivascular cells identify a major source of profibrotic cells during acute tissue injury. Nat Med 2012;18:1262-70. [CrossRef]