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Over the past decades, epidemiologic studies have shown increasing incidence of Congenital Penile Malformations (CPMs)1. Anomalies of the male external genitalia may be confined to the clinical appearance, or might be the first clue indicating further underlying disorders that require evaluation.

Hypospadias is the most frequent congenital penile defect affecting the external male genitalia, with an incidence around one in 250 male newborns2. It is therefore the most studied CPM.

Buried penis (BP) is another CPM frequently encountered in pediatric urology. Although the true incidence of BP is unknown because of an ongoing debate about its definition, BP is probably the most frequent penile pathology after hypospadias3. When BP is observed as a CPM, it is also described as inconspicuous penis, hidden penis, cryptic penis, concealed penis, meagrepreputium with concealed penis, all those terms covering one single pathologic finding: a normal penis is entrapped in pubic fatty tissues, only leaving a redundant preputium visible4-6.

Hypospadias and BP are the most frequent CPM. Many other CPM can however be observed, even if they are very infrequent: aphaelia (absence of penis), diphallia (penile duplication), penile torsion, epispadias (associated with the bladder exstrophy complex or as a stand-alone condition), penoscrotal transposition, ...

Dartos Tissue and Congenital Penile Malformations

Dartos tissue (DT) is considered a superficial fascia, originating immediately under the genital skin, originating in Scarpà’s abdominal fascia, and in Colle’s perineal fascia. It is superficial to Buck’s fascia. The composition of fibromuscular DT along the penis shaft determines elasticity of the subcutaneous tissue and the skin mobility7.

The skin of the penis is highly elastic, and has no hairy elements. This skin is relatively fat free, and mobile because of its loose attachments to the underlying DT. Distally, it folds over itself, thereby creating the prepuvium, or foreskin covering the glans.

The basic observation, during penile surgery, that, in many of the CPM, the DT had a different aspect than the DT in the normal penis, led to the set-up of a research line.

In distal hypospadias repair, release of the fibrotic DT often corrects the ventral curvature, indicating that this tissue plays a role in the pathophysiology of the penile curvature. In BP, it is observed that the penis is entrapped in a cocoon of fibrotic DT. With penis development, and release of penis out of its cocoon, the penile entrapment is resolved, restoring normal penile length8.

Androgens and Congenital Penile Malformations

Male external genital development depends, among others, on the conversion of testosterone by the 5-alpha reductase, produced by the primitive testis from the third week on, into the more active dihydrotestosterone. Some disturbances in male hormonal production or action might be involved in CPMs, as already observed in Disorders of Sexual Development (DSD).

There is an ongoing debate on whether CPMs should be considered a minimal condition in the spectrum of DSD, or should be considered as a completely different pathologic entity. In some DSD conditions like the virilizing form of congenital adrenal hyperplasia, where a 46 XX girl shows male genitals because of androgenic influence, or like complete androgen insensitivity syndrome, where a 46 XY boy has female external genitals, the hormonal influence is clear and quite well understood. In CPM without DSD, the etiologies are not so clear nor understood.

Human male and female genitalia originate from a common identical genital tubercle. Sexual differentiation into male or female starts around the 8th gestational week, under the influence of the Sex-determining Region Y (SRY) gene9,10. With progressive differentiation of the undifferentiated gonad into testicle, androgen production is started, along with Anti-Müllerian Hormone (AMH), allowing further differentiation into male genitalia. Initial differentiation of the bi-potential undifferentiated gonad is androgen-independent until a testicle is formed. Further development of the male genitalia is androgen dependent, while regression of female (Müllerian) primitive structures is dependent on AMH production.

Under the influence of androgens, the genital tubercle grows into the penis6.

One of the questions that arise is whether DT development is hormone-dependent. It is known that the development of the male external genitalia occurs under hormonal influence so it seems logical that disturbances in the hormonal mechanisms can have any influence on DT patterns. In adult urologists, some pathologies are known to be under the direct influence of androgens, like for instance development of prostate cancer. There is a lot of research going on about androgen receptors in pathologic and healthy prostatic tissue, searching there for clues to eventually obtain a better control of the disease.

As the DT is a genital tissue, we would logically expect androgen receptors. Larry Baskin’s team (UCSF) has been producing leading research over the last decade about the possible influence of androgens and their receptors in genital development. They observed genital development in the spotted hyena, a fascinating animal which has the particularity of having extreme masculinization of the female external genitalia11. The spotted hyena is a mammal that mates and gives birth through a dangling penis-like clitoris. Their findings showed early penile development is androgen independent, like human primitive penile development is believed to be12.

Of course, whether those findings can be transposed in humans remains unclear. Few studies have been investigating the possible role of androgens or estrogens in humans10. Initial studies of the same team showed that androgen receptor is overexpressed in boys with severe hypospadias13. This was however observed in a fibroblast cell line derived from neonatal human foreskin in a small series of patient comparing mild hypospadias to severe hypospadias. There are, to our knowledge, no data available exploring the androgen or estrogen receptors in human penis skin, or any other penile tissue.

As environmental pollutants are believed to act like endocrine disruptors that might be at the source of the increased incidence of CPM during the last decades, exploring penile tissues’ androgen and estrogen receptors might provide some clues to completely the CPM puzzle.

Based on this concepts, a research line investigating the role of DT in CPM was created, with androgens influence on this tissue to be discovered.

Setting up a prospective database of children undergoing surgery for CPM

Starting in November 2011, a databank was prospectively created in Ghent University Hospital with tissue samples collected from children undergoing primary penile surgery (PPS) for CPM, with children undergoing circumcision for non-medical reason as control14. This database is to date still prospectively maintained. Ethical approval was obtained.

The collected samples consisted of the successive preputial tissue resected with the underlying DT in case of non-medical circumcision. In hypospadias, the analyzed samples consisted of the hooded prepuce and the DT resected for chordee correction. In BP, the samples consisted of preputial tissue and resected subcutaneous DT as described in our technique based on the anchoring of the stretched penis at its base with residual DT15.

CPM, Dartos Tissue and androgens

At time of the analysis, tissue samples of more than 500 children were included. Indications for surgery were CPM in children: hypospadias primary repair, epispadias and BP. Children undergoing circumcision for non-medical reasons, served as control group.