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Indications of feminizing Surgery in different Causes of Ambiguous Genitalia-A Mini Opinion

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Keywords: Somitomeres; Dermatome; Myotome; Angiotome; Sclerotome; Genital ducts; Estrogens

Abbreviations: DSD: Disorders of Sex Development; CAH: Congenital Adrenal Hyperplasia; AIS: Androgen Insensitivity Syndrome

Introduction

In the 3rd week of GA, onset of human organogenesis starts when the paraxial mesoderm organizes into segments called somitomeres (somites). At that period, 3 germ layers comprising of the ectoderm, the mesoderm and the endoderm causes the development of specific tissues and organs [1]. First somites present in the cephalic region of the embryo at roughly the 20th day of development and their development proceeds cephalocaudal at a rate of approximate 3pairs/day. By the end of 5th wk the embryo has 42-44 pairs of somites, these consist of 4 occipetal, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 8-10 coccygeal pairs [1]. Each somitomere is made up of mesodermal cells arranged in concentric whorls around the center of the units. Somites give rise to 5 components, namely the myotome, (segmental in component), sclerotome (cartilage and bone component), the dermatome (forms the skin of the back). All of these tissues are supporting tissues of the body like myotome and dermatome retains its own innervations and vascularization from its originating segments, and they form the neurotome and angiotome respectively [1,2]. Vertebral column and ribs retain segmental structure. They develop from the sclerotome compartments of the somites and they join in the ventral body wall. Every segment includes all of the following 5 components; a vertebra connected to a rib (sclerotome) with intercostal muscles (myotome) and vessels (angiotome) covered in skin (dermatome). The 1st occipital and the last 5-7 coccygeal somites later disappear while the remaining somites form the axial skeleton [1](Figure 1 a & 1b).

I. To start with the genital system consists of

II. Gonads or primitive sex glands

III. Genital ducts

IV. Indifferent external genitalia.

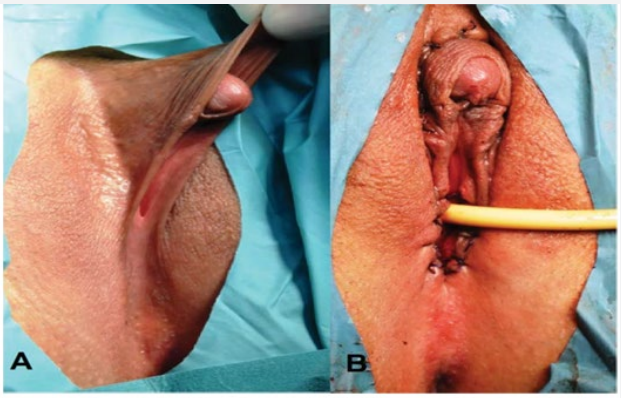

Figure 1a and 1b: Congenital Adrenal Hyperplasia (Prader Dtage III)

A) External genitalia before operation. Clitoromegaly and sinus urogenital is resulted of incomplete posterior labial fusion.

B) External genitalia after clitoro reduction and introitoplasty.

All three go through indifferent stages after which they develop following male or female pathways [1-5]. The organogenesis of the external genitalia proceeds from the 3rd to the 12th wk of embryonic development. During the 3rd wk of development, mesenchymal cells originating around the

primitive streak move to the cloacal membrane to form a pair of slightly elevated cloacal folds. In Cranial aspect of the cloacal membrane, the folds unite to form the genital tubercle. Caudally these folds are subdivided into urethra (anterior) and anal (posterior). In the meantime, a 2nd pair of elevations, known as the genital swelling become visualized on each side of the urethral folds. These swellings later give rise to the scrotal buds in males and labia major a in females. Development of external genitalia in both sexes occurs from genital tubercle, genital swellings and genital folds. By the end of the 6th week the genital tubercle is indistinguishable between males and females [1]. Both the indifferent duct system and external genitalia develop under the influence of hormones. In males the SRY gene present on the Y chromosome produces testis determining factor and regulates male sexual development. Testosterone produced by testicular leydig cells stimulates the development of the mesonephric duct into the vas deferens and epididymis. Dihydro testosterone stimulates development of male genitalia/ virilization, which consists of penis, scrotum and prostate. The genital tubercle elongates to form the penis (phallus), and the penile urethra, which terminates into glans penis. The prostate forms in the walls of the urogenital sinus (Figure 2).

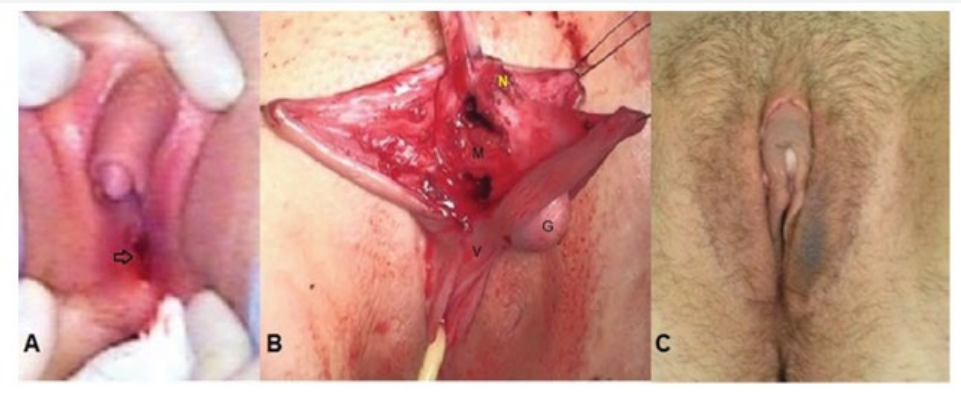

Figure 2: 46,XY gonadal (testicle) dysgenesis, incomplete form.

(A) External genital view before operation. Clitoromegaly (appr. 5-6 sm), corresponds to Prader stage III-IV. The vagina introitus normal corresponds to Prader 0 (arrow).

(B) The stage of clitororeduction: separated glans clitoris connected with dorsal (N) and ventral (V) neurovascular bundles; corpora cavernosa clitoridis (V).

(C) The external genitalia after clitoro reduction by recection of corpora cavernosa, in 3 week after operation.

In the absence of inactivity of androgens, the fetus remains in the indifferent stage and becomes phenotypically female. Estrogens stimulate the development of the external genitalia in female. In female the genital tubercle becomes the clitoris, the genital swellings become the labia major, and the genital tubercle elongates slightly and forms the clitoris which is longer than in the male in the early stages of development. The (urethral folds do not fuse as occurs in the male embryo and develops into labia major. The urogenital groove remains open and forms the vestibule vagina [1-6]. During embryogenesis if there are abnormal androgen effects they cause persistence on between developmental stages ,which may result in the fetus clinically presenting as intersexual (DSD), or it could result in the fetus developing and being assigned female sex at birth [7-16]. Disorders of sex development (DSD), or intersexuality (or ambiguity) are present in 0.018% (1.8/10,000 live births(of newborns and the incidence of 46XY DSD is estimated at 1 in 20,000 live births. >than 90%of 46XX patients (congenital adrenal hyperplasia (CAH) and 46XYDSD patients (androgen insensitivity syndrome, testicle dysgenesis) are assigned as females required for feminizing plasty [7,8].

Feminizing genital surgery is considered in cases of severe virilization (Prader stages III-V). Prader classification of ambiguous external genitalia includes the following

Prader Stage 0

Corresponds to females having normal external genitalia. This includes females with 45X/46XX Turner Syndrome and those with a complete form of 46 XY gonadal dysgenesis and androgen insensitivity syndrome (AIS), who present with feminizing externally.

Prader Stage I

Is characterized by a slightly enlarged clitoris. Prader Stage I may be regarded as a common condition present in the general female population.

Prader Stage II

Distinguishes a mild degree of virilization and does not need surgical correction.

Prader Stage III

V is recognized as ambiguous genitalia or intersex DSD. Patients with ambiguous genitalia (Prader Stage III–V) undergo feminizing genitoplasty according to the European Consensus recommendations.

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Prader Stage IV

Indicates a normal presentation with typical external genitalia and normal testis in the scrotum.

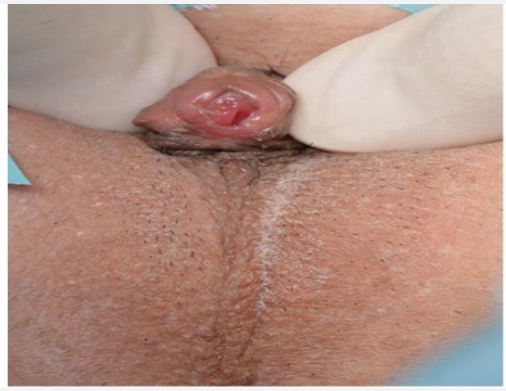

Figure 3: 46,XY gonadal (testicle) dysgenesis. External genitalia corresponds to Prader stage V. Micropenis and complete labial fusion to penile (masculine) urethra.

Surgery should be performed with the introitoplasty of the common urogenital sinus [9-18]. Surgical procedures should be anatomically based to preserve the clitoris innervations, which possesses erogenous sensation and orgasmic function [17] (Figure 3). Addressing the management of intersex disorders in a standardized fashion and investigating the development of genital tubercle, Makiyan 2016 examined 114 pts with different forms of DSD in which ambiguous genitalia (bisexual) external genitalia was found 73patients and 51 of whom underwent feminizing surgery. Intersexuality i.e, ambiguity in 46XY patients occurs due to disruptors in the pathway of sex steroid hormones or receptors while in 46XX females it occurs due to increased levels of androgens. Systematization of intersex disorders can differentiate the karyotype, gonadal morphology and genital anatomy to get a differential diagnosis and guide proper surgical management. Modified feminizing clitoroplasty with preservation of the dorsal and ventral neurovascular bundles for retaining erogenous sensitivity was done in females with severe virilization (Prader degree III-V). The outgrowth of the genital tubercle and the fusion of urethral folds occurred in an ordered fashion, but in some cases of ambiguity, there was discordance due to different pathways. Previously it was speculated that the genital tubercle derives from these 3 layers namely, the ectodermal glans of the tubercle, the mesodermal corpora cavernosa and the endodermal urogenital groove. According to the new hypothesis given by Makiyan 2016, during the indifferent stages the 5 sacral somites have to recede from their segmentation and disintegrate; the sclerotome from the pelvic bones, the fused myotomes follow with their genuine neurotomes and the angiotomes join the corpora cavernosa of the genital tubercle. Sexual differentiation of external genitalia is final in gender embryogenesis but surprisingly derivation of the indifferent genital tubercle from 5 somites occurs before gonadal and internal organs development [19].

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