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"EXSTROPHY-EPISPADIAS COMPLEX" EMBRYOLOGICAL BASIS AND ITS CLINICAL SIGNIFICANCE

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ABSTRACT

The term exstrophy-epispadias is mainly coined due to the group of congenital abnormalities such as, bladder-exstrophy and cloacal-exstrophy. Because of the presence of abnormal opening into the cloaca, all embryos were considered by an abnormal widening of caudal trunk at the level of the leg buds which, in the youngest embryos, was associated with the abnormal presence of large aneurysmatic swellings of the dorsal aortae at this side

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Introduction

The Exstrophy-Epispadias complex (EEC) is the most critical form of abdominal midline deformity with defects involving the urinary system, the musculoskeletal system, the pelvis, the pelvic floor, the abdominal wall, the genitalia and sometimes the spine and the anus. The severity level ranges from epispadias representing the mildest form, with lower and upper fissure, to a classical bladder exstrophy (CBE), and exstrophy of the cloaca (EC) which is often referred to as OEIS (omphalocele, exstrophy, imperforate anus and spinal defects) complex the most severe form. there are two forms of EEC, classical or typical EEC and atypical EEC(pseudo-exstrophy). Muecke In 1964 was the first to report that mechanical disruption or enlargement of the cloacal membrane in chicks prevents the interruption of mesodermal cells along the infra umbilical midline, by that results in exstrophy [1,2]. Based on Muecke, Austin et al. provided evidence that EEC is also in humans, the anomalous growth of the cloacal membrane is associated with exstrophy of the bladder. The congenital anomaly of exstrophy bladder not only involves the urogenital system but also involves the musculoskeletal system of lower abdomen and pelvis. Most of the cases involves a small and bifid penis, which requires surgery for closure soon after birth, also including a reconstruction of the urethra [3]. Bladder exstrophy is a very rare congenital anomaly in which the bladder and other related structures are turned inside out. The posterior portion of the bladder wall (vesical wall) turn outwards (exstrophy) through an opening in the abdominal wall and urine is excreted via this opening [4].

The rage of the exstrophy depends upon the size of opening. The mildest form is when there is a defect in the tube that brings urine out of the body from the bladder (urethra) is termed as epispadias [5]. The Exstrophy of the bladder, cloacal-exstrophy complex is caused by a developmental abnormality that occurs four to five weeks after fertilization in which the cloacal membrane is not replaced by tissue that forms the muscles of the abdomen [6]. The epispadias defect in both sexes results from a developmental abnormality in respect to non-closure of the urethral plate and also in an abnormal dorsal urethral site. Therefore, in males an ectopic meatus or a mucosal strip is present on the penile dorsum and in females a variable cleft of the urethra is determined [7].

According to the meatal site, epispadias is distinguished as peno-pubic, penile or glandular in males. In females, epispadias is divided into three forms according to Davis, either less severe with a gapping meatus, intermediate or severe followed by a cleft including the whole urethra and the bladder neck, also showing bladder mucosal prolapsed [8,9].

Incidence

The incidence of Exstrophy-epispadias complex according to reports varies, primarily in respect to various subtypes, the male-to female ratio and different ethnic groups. Almost 1 in 10,000 births have been affected by the EEC spectrum.[10] Males have been found to be highly affected by this complex than females, with a ratio ranging from 1.5:1 to 6:1. The International clearinghouse for birth defects monitoring systems appraised an average of 2.4 per 100,000; among the 148 cases included, only 4 were females for epispadias. However, most of the incontinent females remain undiagnosed.[11] In Europe the rate ranges from 0.6 per 100,000 in France to 4.7 per 100,000 in Denmark. The highest rate has been observed in Native American Indians.[12]

The incidence of Cloacal-exstrophy bladder [CBE] reported from 2.1 to 4.0 per 100,000 births. The incidence of CBE varies according to the geographic region and socioeconomic status and is more frequent in white infants. In a survey from 198 to 1999 in the New York State a strong association between the white, non-Hispanic maternal ethnicity and the CBE was found.[13]

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EEC has been reported more commonly in females with a prevalence rate ranging from 0.5 to 1 per 200,000 live births. This was confirmed by the New York State survey, finding associated risk factors like low birth weight, preterm birth and non-New York City residence.[14] EEC seems to be under-estimated in still born, and therefore have a higher incidence ranging from 1 in 10,000 to 1 in 50,000.[15]

Ontogenesis for normal urinary system

The urinary system development as a part of the prenatal development, concerns the urinary system and sex organs. The later is a time of sexual differentiation stages.

The source of development of urinary system and reproductive organs is intermediate mesoderm. The permanent organs of the adult are introduced by a group of structures which are purely embryonic, and with the exception of the ducts which almost disappear before the end of fetal life. These embryonic structures are on both side;the pronephros,the mesonephros and the metanephros of the kidney, and the Wolffian[mesonephric ducts] and Mullerian ducts[paramesonephric ducts] of the sex organ. The pronephros disappears very early; the structural elements of the mesonephros mostly degenerate, but the gonad is developed here, with which the mesonephric duct remains as the duct in males, and the paramesonephric duct as that of the female. Some of the tubules of the mesonephros forms the part of permanent kidney.

Ontogenesis of exstrophy epispadias complex [EEC]:

Based on the developmental study of hereditary anorectal malformations in animal embryos, it has been winded up that agenesis of the dorsal part of the cloacal membrane forms the basis of congenital malformations of cloaca-derived orifices such as epispadias, hypospadias, bladder and cloacal exstrophy, double urethra, and cloacal membrane agenesis. [16]Also, Thomalla et al. created a herniation of the lower abdominal wall of chick embryos by incising the cloacal membrane with a laser.[17] The resulting chicks were born with exstrophy, hence aiding the idea of premature rupture of the cloacal membrane. The resulting variant of the EEC is determined by the timing of disruption of the cloacal membrane, with an earlier disruption before fusion of the urorectal septum to the cloacal membrane i.e., between 4-6 gestation weeks leading to the more severe exstrophy.[18] Therefore, rupture of the cloacal membrane just after the descent of urorectal septum is completed after 6 weeks but before the initiation of genital tubercle development of embryological life is the cause of EEC.[19] There is a strong association between the mechanical obstruction of mesoderm migration to the lower ventral abdominal wall and the unusual caudal insertion of the body stalk. This results in the failure of usual mesodermal interposition in the lower midline.[20,21]

The umbilical cord directly adjoins the cloacal membrane and the superficial unstable cloacal membrane is vulnerable to rupture in this case.[22] Adding to mechanical disruption, increase in cell death locally reduces the population of ventral mesenchymal cells leading to infra-umbilical midline defaults like EEC.[23,24] The use of antibiotics like nigericin also increases the incidence of this complex.[25]

The central feature of this anomaly is the abnormal persistence of the caudal position of the insertion of the body stalk on the embryo. As a consequence of this, the normal interpositioning of mesenchymal tissue to the midline becomes impossible.[26,27] The cranial end of the cloacal membrane remains in contact with the inferior aspect of the low-set body stalk and the cloaca cannot be translocated backwards into the body cavity. This, in contrast to the previously proposed abnormal rostral extension of the cloacal membrane, causes a wedge-effect resulting in the lateralization of the abdominal wall structures and also in the prevention of the midline fusion of the genital hillocks.[28,29,30]

A cloacal membrane normally is an unstable structure lacking mesoderm, and it retains these characteristics in the superficial and infraumbilical position. It has a strong tendency to disintegrate in the early fetal life. It may rupture at variable times and to any extent.[31] The consequence of such an early embryonic event is either a typical bladder exstrophy or one of the variants of the exstrophy malformation.[32,33]

A. Classical Bladder Exstrophy

CBE is characterized by the evaginated bladder plate where urine drips from the ureteric orifices on the surface of bladder. [35]The bladder mucosa is visible and appears reddish at birth[36].Mucosal polyps may be seen on the bladder surface.[37] Delayed closure, further leads to inflammatory or mechanical alterations with signs of mucosal inflammation such as ulcerations, a whitish coating, and hyperplastic formations[38,39] . The transition junction is marked by the paraexstrophic shining thin skin stripes between the squamous metaplastic area and the normal skin. Umbilical hernias and rectal diastasis and can be palpated below the low situated umbilicus. On both sides of the bladder template the pubic bones can be felt at the distal end of the triangular edges. In most patients of both sexes bilateral inguinal hernias are palpable [40].

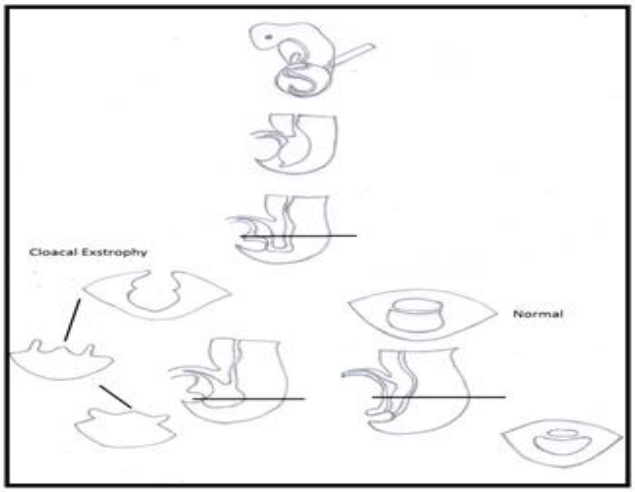

Fig 1. Normal and abnormal bladder formation.

B. Male Genitals in Classical Bladder Exstrophy

In males, an epispadias, open urethral plate from the open bladder to the glandular grove covers the whole dorsum of the penis.[41] Beneath the urethral plate both corpora cavernousa are located. Careful examination reveals tiny openings of colliculus-seminalis and ductus ejaculatorii, where the prostate is apparently located. [42]The penis appears curved dorsally and shorter than normal. The testes are normal-sized usually located in the scrotum.[43]

C. Female genitals in classical bladder exstrophy:

In female infants, an entirely split clitoris can be seen next to the open urethral plate[44]. The vaginal opening is narrow and anteriorly placed on the perineum. The perineum is shortened as the anus is ventrally positioned.[45]

D. Epispadias in both sexes

This defect in both sexes results from a developmental obstruction in terms of failure of the urethral plate to close and additionally in an unusual dorsal urethral location.

Therefore, in male infants a mucosal strip or an ectopic meatus is found on the penile dorsum and in female infants an irregular cleft of the urethra is spotted.[46,47] In males according to the location of the meatus, epispadias is distinguished as either penile, penopubic or glandular.[48] According to Davis episapdias in females, is divided into three degrees, either less severe with a gaping meatus, intermediate or severe with a cleft involving the bladder neck and the whole urethra, additionally exhibiting bladder mucosal prolapse.[49,50] Rectus anatomy and abdominal wall, as well as the umbilicus, are completely normally developed. The symphysis is closed or only a minor symphysis gap is palpable in both sexes, indicating only minor pelvic floor anomalies. The main clinical symptom appears to be urinary incontinence, due to involvement of the urinary sphincter.[51,52] In most distal epispadias, involuntary urine loss is not found, whereas in complete epispadias urine drips permanently through the meatus in both sexes. Due to minor clinical abnormalities, distal epispadias might be overlooked at birth, especially in girls which is then diagnosed later in school age, due to urinary incontinence.[53]

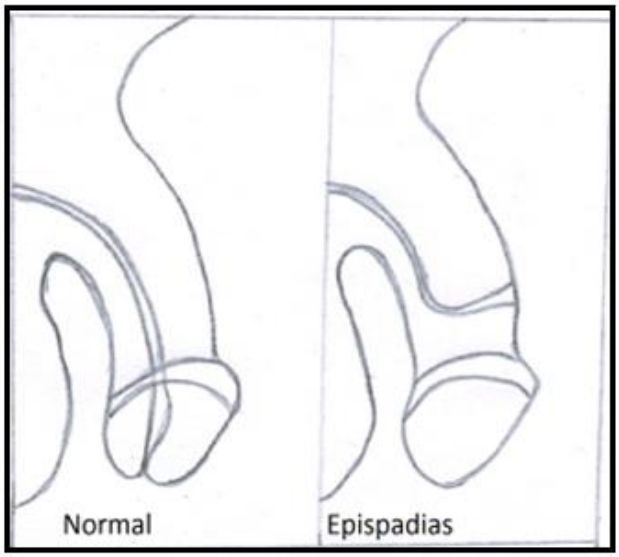

Fig 2. Epispadias in male.

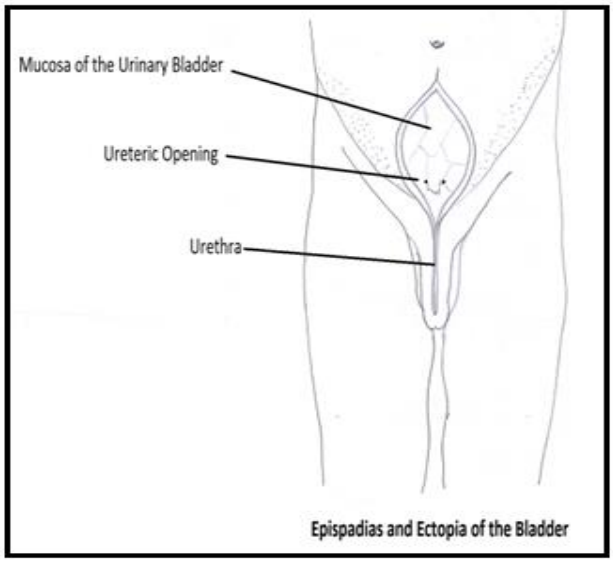

Fig 3. Epispadias in female.

Discussion

Muecke (1964), was the first to report that enlargement of the cloacal membrane or mechanical disruption in chicks prevents the invasion of mesodermal cells along the mid-infraumbilical line, and thereby results in exstrophy.[54] On the asis of that, Austin et al. provided evidence that in humans, bladder exstrophy is associated with overgrowth of the cloacal membrane. Animal models of EC support the idea that abnormal partitioning of the cloacal membrane causes displacement of the genital tubercle and therefore resulting in epispadias formation. [55,56]Accordingly, on the basis of a embryological study of hereditary anorectal malformations in animal embryos, it has been concluded that the basis of congenital malformations of cloaca-derived orifices such as hypospadias, epispadias, bladder and cloacal-exstrophy, double urethra, and cloacal membrane agenesis may be formed by the agenesis of the dorsal part of the cloacal membrane.[57,58] In addition to it, Thomalla et al. created a hernia defect of the lower abdominal wall of animal embryos by incising with a laser on the cloacal membrane. The resulting animals were born with EEC, hence supporting the idea of premature rupture of the cloacal membrane.[59] Molecular and cytogenetic analyses have revealed chromosomal anomalies in 20 EEC patients to date, although none of these appear to be causative. In six patients numerical chromosomal aberrations were observed. In a further four CBE males, one CBE female and one female with EC, an association with Down syndrome was found.[60,61] The authors postulated that EEC would form if cloacal membrane rupture occurred just after the urorectal septum completed its descent but before the initial formation of the genital tubercle.[62] Mechanical obstruction of mesoderm migration has also been associated with abnormal caudal insertion of the body stalk, resulting in failure of the normal mesodermal interposition in the lower midline.[63] In this case, the umbilical cord is directly adjacent to the cloacal membrane, and the superficially placed, unstable cloacal membrane is prone to rupture.[64,65] Additional to mechanical disruption, localized alterations in cell death may reduce the ventral mesenchymal cell population and therefore lead to infra-umbilical midline deficiencies in animlas, including EEC.[66] Another totally different mechanism for the organogenesis of CBE is postulated by the observations of the pelvic development in animal embryos, relating pelvic bone and bladder anomalies in temporal-spatial development.[67]This novel mechanism occurs as early as secondary gastrulation without any involvement of the cloacal membrane. In additionto it, two reports describe the incidence of EEC in chicken embryos succeeding the administration of nigericin and ochratoxin A.[68,69]

In both sexes, urological malformations such as ureteropelvic junction obstruction, ectopic pelvic kidney, renal hyo- or agenesis, horseshoe kidney, megaureter, ureteral ectopy and ureterocele exist in about one third of all EEC cases, predominantly in the EC population.[70,71] However, due to a developmental failure of the ureterovesical junction a 100% prevalence of bilateral vesicoureteral reflux throughout the EEC spectrum warrants an antireflux procedure with every bladder neck plasty.[72]

The incident occurrence of spinal anomalies widely varies within the EEC spectrum.[73] Spinal anomalies occur in about 7% of cases in children born with CEB, whereas a heterogeneous group of congenital spinal anomalies resulting from anomalous development of the caudal cell mass and defective closure of the neural tube early in fetal life can be confirmed with magnetic resonance imaging (MRI) in nearly 100% of EC patients.[74,75] Therefore, newborn EC patients should have spinal radiographs and ultrasound to define the individual spinal anomalies ranging from hemivertebra to

myelomeningocele.[76,77] MRI is further recommended in follow-up to identify occult spinal cord abnormalities predisposing to spinal cord tethering.[78].Additionally, a neurological component must be kept in mind in EC in respect to bladder function, lower extremity function and aerectile capacity.[79,80].

In EC, limb and skeletal abnormalities such as clubfoot deformities, absence of feet, fibular or tibial deformities, and hip dislocations are commonly seen. [81]The fundamental impact for all EEC patients in addition to the clinical examination is a sonographic evaluation of the hip joints.[82,83] When planning operative reconstruction of the pelvis management even if conservative should be kept in mind.[84] To estimate the dimension of the symphysis gap and the hip localization a plain pelvic X-ray can be helpful.Gastrointestinal tract abnormalities will seldom be present in CBE or Epispadias and are predominantly associated with EC.[85]Omphaloceles are found in 88-100% of cases in EC in addition to a common hindgut remnant of varying size. Gastrointestinal duplication or malrotation, as well as short bowel syndrome, can be seen in up to 46% of cases[86]. An either anatomical or functional short bowel syndrome causes absorptive dysfunction in about 25% of cases.[87].On rare occasions, small bowel deletion and duodenal atresia have been described in EC[88]. Thus, the gastrointestinal tract significantly contributes to the morbidity in EC.In addition to the external female genitalia anomalies, the cervix inserts low down at the superior vaginal wall close to the introitus in most cases[89,90].

The Anatomy and function of the adnexae and the uterus are normal. However, the levator defect and the pelvic floor, together with the absence of the cardinal ligaments, predispose women to uterine or vaginal prolapse in as high as 50% of cases[91,92]. Müllerian anomalies are quite common in EC; respectively, duplication of the uterus and vagina, as well as vaginal agenesis has been reported.[9,94]

Conclusion

The primary management is surgery, with the main aims of obtaining secure abdominal wall closure, achieving urinary continence with preservation of renal function, and, finally, adequate cosmetic and functional genital reconstruction. Counseling should be provided to parents but, due to a reasonable outcome, termination of the pregnancy is no longer recommended. Several bladder reconstruction methods with creation of an outlet resistance during the infancy are favored worldwide. Removal of the bladder template with total urinary diversion to a rectal reservoir can be chosen as an alternative. After the reconstructive surgery of the bladder, continence rates of about 80% are expected during early childhood. Additional surgery might be needed to increase the efficiency of bladder storage and emptying function. In cases of final reconstruction failure, urinary diversion should be done. In puberty, reproductive and genital functions are important issues. Psychosocial and psychosexual outcome depend on long-term multidisciplinary care to facilitate an adequate quality of life.

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