A Clinical, Anatomical, Histological and Genetic Study of Exstrophy-Epispadias Complex

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Abstract: Classical exstrophy bladder, epispadias, cloacal exstrophy constitute a rare spectrum of anomalies. The incidence and prevalence of these anomalies with the inheritance pattern was observed in accordance with the available previous studies. The clinical features and exact urological complaints with regard to other associated malformations were recorded in present study comprising of six male patients (age group 0 to 6 years). Investigations like IVP showed small bladder with vescicoureteric reflux and skeletal shadow shows prominent pubic diastasis. The surgical corrective procedures with adequate follow up was done together with histological study of the biopsy specimens from the bladder mucosa which revealed normal transitional epithelium with no cystic or metaplastic changes. Karyotype was normal (46XY) and chromosomal malformations could not be accounted. Genetic counseling of parents was done and prenatal diagnosis for future childbirths was advised.

Key words: Bladder exstrophy, Epispadias, Cloacal exstrophy

Introduction:
The congenital abnormalities of the lower urinary tract constitute a sizeable problem in urological studies both of interest to the surgeon and the anatomist – of which bladder exstrophy, epispadias and cloacal exstrophy are a very rare spectrum of anomalies.

The data from the International Clearinghouse for Birth Defects monitoring system estimated the incidence of bladder exstrophy to be 3.3 cases in 1,00,000 live births, Lancaster (1987). The male-to-female ratio of bladder exstrophy derived from multiple series is 2.3:1, Shapiro et al (1984). The risk of recurrence of bladder exstrophy in a given family is approximately 1 in 100, Ives et al (1980).

Male epispadias is a rare anomaly with a reported incidence in 1 in 1,17,000 males. Most male epispadias patients (about 70%) have complete epispadias with incontinence, Gearhart and Jeffs (1998). Penile deformity is virtually identical to that observed in bladder exstrophy. The reported male to female ratio of epispadias is 5:1, Krammer and Kelalis (1982a).

Cloacal exstrophy represents one of the most severe congenital anomalies compatible with intrauterine viability. It is exceedingly rare, occurring in 1 in 2,00,000 to 4,00,000 live births, Hurwitz et al (1987). Most recent reports indicate a male–female sex ratio of 2:1, Gearhart and Jeffs (1998). According to Muecke (1964), an abnormally extensive cloacal membrane produces a wedge effect, serving as a mechanical barrier to mesodermal migration, which results in impaired development of the abdominal wall; failure of fusion of the paired genital tubercles and diastasis pubis. Exstrophy of the cloaca results when wedge effect occurs before the formation of urorectal septum at 6 weeks.

The aims and objectives of this study was to observe the entire clinical spectrum of these anomalies with respect to a detailed maternal and family history of the children encountered (age group 0 to 6 years), histological study of the biopsy specimens obtained and genetic study through karyotyping. The surgical corrective procedures were done with adequate follow up. Genetic counselling of the parents of the children in this study was also done.

Material And Methods:
The present study was conducted in the Department of Anatomy, IPGME&R, and SSKM Hospital, Kolkata. Six male patients (between the age group 0-6 years) came to the Paediatric Surgery and Urology OPD, SSKM Hospital, Kolkata, with the clinical signs and symptoms of bladder exstrophy – epispadias complex and cloacal exstrophy, which provided the necessary clinical material for our present study. The patients were divided into the three groups: Type I – Patients presented with classical bladder exstrophy with epispadias. No. of patients seen – 3. Type II - Patients presented with only epispadias (and variable length of dorsal chordee). No. of patients seen – 2. Type III - Patients presented with cloacal exstrophy. No. of patients seen – 1.

Each patient in this study was reviewed according to the following protocol:
A. History
   b. Nature and duration of urological symptoms
   c. Associated symptoms, if any.
   b. Antenatal history
   i) history of intake of drugs like antibiotics, oral contraceptives.
   ii) history of exposure to TORCH agents, diabetes
   c. Obstetric history
      i) parity
      ii) history of recurrent abortions (if any)
      iii) history of present childbirth
3. Family history.

B. Clinical Examination
1. Local examination: With special emphasis to find out the exact nature of urological defects
2. Systemic examination: to search for associated anomalies in, musculoskeletal, neurological, cardiovascular and respiratory

C. Investigations:
1. Routine haemogram, serum urea, creatinine and electrolyte levels.
2. Urine for R/E, M/E and C/S.
3. Intravenous pyelogram: was the sheet anchor to visualize the entire urinary tract.
4. Ultrasonography (of abdomen and pelvis) for associated anomalies
5. Echocardiography: for cardiovascular malformations

D. Surgical Corrective Procedures
E. Histology Of Bladder Mucosa
F. Genetic Study Of Patients Through Karyotyping.
G. Genetic Counselling
H. Prenatal Diagnosis

Observations:
Details given in Table No. 1

Table -1

<table>
<thead>
<tr>
<th>Pt Sl. no.</th>
<th>Disease</th>
<th>History</th>
<th>Clinical Findings</th>
<th>Investigations</th>
<th>Surgery</th>
<th>HPE</th>
<th>Karyo-</th>
<th>G/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt. Sl. no.</td>
<td>P/H (age + C/C)</td>
<td>History</td>
<td>Clinical Findings</td>
<td>Investigations</td>
<td>Surgery</td>
<td>HPE</td>
<td>Karyo-type</td>
<td>G/C</td>
</tr>
<tr>
<td>1</td>
<td>B1 Ex + Epi</td>
<td>1m, dribb. of urine</td>
<td>19y, P1+0, FTND</td>
<td>Not sig. B1 Ex, trig with urt orif, Epi, Epi, Ing hernia (R)</td>
<td>NA</td>
<td>IVP-small B1, Others-normal, pubic diastasis CU-VUR USG - NAD ECHO - NAD</td>
<td>Repair of B1 Ex, iliac osteotomies, dorsal chordree repair, herniotomy (R)</td>
<td>Normal trans. epith</td>
</tr>
<tr>
<td>2</td>
<td>B1 Ex + Epi</td>
<td>2m, dribb. of urine</td>
<td>18y, P2 +1, FTND OCP intake till 1st trip</td>
<td>do sig. B1 Ex, trig with urt orif, Epi, Epi, Ing hernia (R) umb hernia</td>
<td>NA</td>
<td>IVP-small B1, Others-normal, pubic diastasis CU-VUR USG - NAD ECHO - NAD</td>
<td>Repair of B1 Ex, iliac osteotomies, dorsal chordree repair, inguinal herniotomy (R), repair of umb. hernia</td>
<td>Normal trans. epith</td>
</tr>
<tr>
<td>3</td>
<td>B1 Ex + Epi</td>
<td>2m, dribb. of urine</td>
<td>21y, P1+1, LUCS, IUGR, Gest Diab</td>
<td>do sig. B1 Ex, trig with urt orif, Epi, Epi, Umb hernia (R)</td>
<td>NA</td>
<td>IVP-small B1, Others-normal, pubic diastasis CU-VUR USG - NAD ECHO - NAD</td>
<td>Repair of B1 Ex, iliac osteotomies, dorsal chordree repair, repair of umb. hernia</td>
<td>Normal trans. epith</td>
</tr>
<tr>
<td>4</td>
<td>Epi</td>
<td>15m, dribb. of urine</td>
<td>23y, P1+0, FTND</td>
<td>do Epi.</td>
<td>NA</td>
<td>USG - NAD ECHO - NAD</td>
<td>Correction of dorsal chordree</td>
<td>Not done</td>
</tr>
<tr>
<td>5</td>
<td>Epi</td>
<td>18m, dribb. of urine</td>
<td>25y, P2+0, FTND</td>
<td>do Epi</td>
<td>NA</td>
<td>USG - NAD ECHO - NAD</td>
<td>do</td>
<td>Not done</td>
</tr>
<tr>
<td>6</td>
<td>C1 Ex</td>
<td>21d, dribb. of urine faeces</td>
<td>20y, P4+0, LUCS</td>
<td>do B1 Ex, RVF</td>
<td>NA</td>
<td>IVP - small B2, others normal USG-NAD ECHO-NAD</td>
<td>Repair of B2 Ex &amp; RVF, Int anast with ileostomy</td>
<td>NAD</td>
</tr>
</tbody>
</table>

Result and Discussion:

The clinical picture of these anomalies comprises a cluster of features.

In type 1 patients, with bladder extrophy-epispadias complex, (Fig. 1) all the three male neonates presented with exstrophied bladder mucosa and epispadias. Repair of bladder mucosa was done in these patients with correction of dorsal chordee and closure of infraumbilical anterior abdominal wall defect combined with bilateral iliac osteotomy, to correct pubic diastasis. Bladder neck reconstruction with anti-vesicoureteral reflux mechanism was advised at the age of 5 years when bladder filling capacity would reach an optimum level. Two patients had right sided indirect inguinal hernia which was corrected by herniotomy and tightening of fascia transversalis.

In patients seen with classical bladder extrophy, pubic diastasis (Fig. 4) was a prominent feature as a radiological finding, but these deformities could not be accurately measured in the neonate as was successfully done by Sponseller et al (1995).

Complete dissection of the bladder neck with flattened puborectal sling of levator ani was done to achieve the pelvic position of the bladder at the time of exstrophy closure. Two of the exstrophy bladder patients had small umbilical hernia which was repaired during closure.

Indirect inguinal hernia was present due to persistent processus vaginalis, and poorly developed abdominal wall. Connelly et al (1995) in a review of 181 children with bladder exstrophy reported inguinal hernias in 81.8% boys and 10.5% girls.

The penis appeared short not only because of diastasis of pubic symphysis, but also because of marked congenital deficiency of anterior corporal tissue as also found by Silver et al (1997b). The ureterovesical junction is inherently deficient in complete epispadias and the incidence of reflux has been reported in a number of series to be between 20% and 40% Krammer and Kelalis (1982a) and Arap et al (1988).

In type 2 patients with only epispadias (Fig. 2) no other associated anomalies were found. So correction of dorsal chordee with epispadias repair was done in both patients.

In the type 3 patient with cloacal exstrophy, (Fig. 3) repair of the exstrophied bladder mass was done with correction of intestinal defect (caecum with terminal ileum) by ileostomy. The rectovesical fistula was closed keeping the site for future anal opening. Care was taken to monitor the electrolyte levels as that could otherwise enhance patient mortality. The patient was asked to come for regular followup. Bladder neck reconstruction with antireflux procedures would follow at the age of 5 years.

No associated anomalies were encountered in our case of cloacal exstrophy. In a large review of cloacal exstrophy cases by Diamond (1990), associated anomalies were seen in multiple organ systems namely spina bifida, meningocele and upper urinary tract anomalies.

Patients had pubic diastasis and widely separated innominate bones for which bilateral iliac osteotomy was done to prevent waddling gait in future. Skeletal and limb anomalies were reported by Diamond (1990) in 12% to 65% of cases.

Since recognition of metabolic changes occurred in patients with ileostomy, an attempt was made to use the hind gut remnant to provide additional length of bowel for fluid absorption, as suggested by Matthews et al (1998). Urinary incontinence was present in most children and required bladder augmentation with use of intermittent catheterization.

Parents of these children in this study were advised sonographic imaging of the foetus as a part of prenatal diagnosis in subsequent conceptions as suggested by Austin et al (1998).

Though omphalocele is frequently associated with cloacal exstrophy, we did not encounter that in our case. The perineum was short and broad and anus was situated directly behind the urogenital diaphragm, a finding noticed during the surgical correction of the rectovesical fistula.

Patients were advised to undergo cystoscopy and cystography at yearly intervals to detect bilateral reflux in almost 100% of patients and to provide an estimate of bladder capacity as also recommended by Gearhart and Jeffs (1998).

Histology (Fig. 5) of bladder mucosa obtained on biopsy did not reveal any squamous metaplasia or cystic changes as neonates were not exposed to considerable surface trauma. The exposed mucosa was covered with protective membranes and irrigated with normal saline prior to surgery.

Karyotype (Fig. 6) of these patients however revealed normal chromosomal pattern, 46 XY. However, genetic counseling of the parents of these patients was done with emphasis on prenatal screening of such anomalies for future child births.
Fig. 1: Classical Exstrophy of Bladder with Epispadias

Fig. 2: Epispadias Only

Fig. 3: Cloacal Exstrophy
The family history and examination of siblings of our patient study could not provide any highlights on the inheritance pattern of bladder exstrophy. Shapiro et al (1985) studied the inheritance pattern extensively in identical and nonidentical twins and found both male and female twins affected in varying proportions. He also determined the risk of bladder extrophy in offsprings of individuals with bladder extrophy and epispadias as 1 in 70 live births, 500 fold greater incidence than in the general population. Inheritance of cloacal extrophy is unknown, because offsprings have never been produced with this disorder.

The mother of the cloacal extrophy patient was reported as para 4+0. In a multinational review of extrophy patients Lancaster, (1987), two interesting trends were found: (1) bladder extrophy tends to occur in infants of younger mothers and (2) increased risk at higher parity is observed for bladder extrophy but not for epispadias.

References: