Original Article

Cloacal Exstrophy: A Histomorphological Analysis of the Bladder Plate and Correlation with Bladder Dynamics


1. Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi-110029, India
2. Department of Pathology, All India Institute of Medical Sciences, New Delhi-110029, India

Abstract. Objective: Physiological outcomes in patients of cloacal exstrophy are governed primarily by neurological innervation and detrusor histomorphology. An evaluation of the bladder plate histomorphology for the presence of neural elements, collagen fibres and smooth muscle components was done and correlation attempted with detrusor physiology. Methods: From three cases of cloacal exstrophy, full thickness biopsies were taken from the bladder plate at the time of single stage total reconstruction and slides stained with hematoxylin and eosin, masson's trichrome and immunohistochemical staining done with S-100, SMA and CD-117. Bladder biopsy taken at the time of cystolithotomy from a child with vesical calculus served as a control. Results: Cloacal exstrophy bladders showed squamous metaplasia, submucosal edema, increased collagen in the muscle layer and poor staining with S-100 (neural elements) and CD-117 (interstitial cells). Whereas the control biopsy showed normal transitional epithelium, good muscle layer with presence of both neural elements (S-100) and interstitial cells (CD-117). Conclusion: Poor muscle layer with increased fibrosis and scarcity of neural elements in the bladder wall may account for the poor compliance of such bladders and explain the incontinence and upper tract deterioration due to high intravesical pressure.

Keywords: Bladder plate, Cloacal exstrophy, Collagen, Histomorphological analysis, Metaplasia

Received: 20 January 2014 / Accepted: 22 January 2014

Introduction

Cloacal exstrophy is a rare congenital paediatric urological problem, the management of which continues to challenge the paediatric surgeons not only for anatomical optimisation but also for improving the long term outcomes and quality of life-social, psychological, physical and physiological. It is the extreme end of a spectrum of defects that can occur in the formation of the ventral abdominal wall and represents one of the most severe anomalies that is compatible with viability. This entity is extremely rare, occurring in 1 in 200,000-400,000 live births.[1-3] The male to female ratio has most recently been reported in a large contemporary study to be equal between the sexes, 1:1.[4]

The goals of surgical reconstruction in these patients are to correct the urogenital and gastrointestinal defects providing a reservoir that is adequate for urinary storage at low pressures with the ability to empty completely without compromising renal function, to create functional and cosmetically acceptable external genitalia, and to maximizing patient quality of life. Urodynamics in such cases is governed primarily by two entities-the neurological innervations and the detrusor histomorphology. Neurospinal abnormalities have been noted in 85-100% of patients with cloacal exstrophy with a distribution of lumbar (80%), thoracic (10%) and sacral defects (10%).[5] The presence of a significant neurologic deficit is associated negatively with the ability to develop continence.[6] Various authors have tried to correlate the detrusor histomorphology with muscle contractility in bladder exstrophy patients and few cases have been similarly reported for cloacal exstrophy.[7-8]

We have, here, attempted to correlate the histomorphological findings with neurological outcomes in terms of increase in capacity and detrusor contractility over time.

Materials and Methods

Three neonates presented to our department over a period of one year from July 2012 - June 2013 with a classical exstrophy of the cloaca. All three underwent single stage total

Copyright and reprint request:
Dr. M. Bajpai, MS, MCh, PhD, FACS, FRCS, FAMS (India), DNB, Fulbright Scholar (USA), Commonwealth Fellow (UK), Raja Rammanna Fellow (India)
Professor, Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi 110029, India, Web: www.paediatric-urologyonline.org; E-mail: bajpai2@hotmail.com; Ph:+91-11-26593555; Mob:+91-981-802-5584
reconstruction of the defect after optimal stabilisation. Intraoperatively full thickness biopsies were taken from the bladder plate and fixed in formalin. Thereafter, slides prepared from the tissue specimen were stained with Hematoxylin-Eosin and Masson’s trichrome stains and immunohistochemical staining was done with S-100, CD-117 (c-kit) and SMA (smooth muscle antigen).

Full thickness bladder biopsy during a cystolithotomy for a primary vesical calculus was used as a control to compare the findings. The distribution of various parameters in the specimen was subjectively analyzed without any definite measurements. An average analysis of the three cases’ histopathological findings was taken.

**Results**

All three cloacal extrophy cases were consistent in their histomorphology with marked variation as compared to the control *i.e.* apparently healthy bladder. In contrast to the normal-looking transitional epithelium of the control (Fig. 1a and Fig. 1c), the mucosa of the bladder plate in the cloacal extrophy cases had squamous metaplasia (Fig. 1b and Fig. 1d). The submucosa showed severe edema and congestion in the cases vis-a-vis mild congestion in the control. The muscle layer contained only healthy muscle fibres in the control (Fig. 1e) whereas both collagen fibres as well as hypertrophied smooth muscle elements constituted the muscle layer in the cloacal extrophy specimens (Fig. 1f).

On immunohistochemical analysis, scarcity of neural elements, as denoted by poor expression of S-100, was noted in the cases (Fig. 2d). Also, interstitial cells were markedly reduced in the cases as visualised on staining with CD-117 (c-kit) (Fig. 2b). SMA staining showed marked hypertrophy of the muscle bundles in the cases. All these findings were in contrast with a healthy muscle layer in the control specimen with adequately present neural elements (Fig. 2c) and interstitial cells (Fig. 2a).

Comparison of the histological findings of cloacal extrophy bladder plate with an apparently healthy bladder tissue is described in table 1.

**Discussion**

Ultrastructural changes in the bladder plate have been looked into in cases of classical bladder extrophy many times in literature. Mathews *et al* obtained bladder biopsies from 32 patients of bladder extrophy at various stages of reconstruction and evaluated them for various histological parameters and found that patients with good parameters had good outcomes in terms of increased bladder capacity with age. They found an increase in the collagen fibres in the muscle layer as well as a decrease in the smooth muscle to collagen ratio stating thereby, that increased collagen is responsible for the decreased compliance of these bladders and their poor ability to ‘catch-up’ their capacity with increasing age of the child.
In the present report, similarly, an increase in the collagen elements was represented by an increase in the Masson’s trichrome staining in the muscle layer of the specimens. It has been reported that kit-positive interstitial cells in the submucosal layer can play a key role in communicating stimulation to afferent nerves in the bladder.\(^9\) Moritoki et al evaluated the bladder plate and hindgut biopsy in a cloacal exstrophy patient and tried to correlate the findings with bladder neuropathic dysfunction. Fewer kit-positive interstitial cells were found in the submucosal layer in the cloacal exstrophy tissue than in the normal bladder tissue. Hence, they hypothesized that fewer neurons and interstitial cells in the bladder submucosa of a cloacal exstrophy patient may be responsible for its neuropathic nature.\(^9\)

Likewise, markedly decreased expression of CD-117 (c-kit) and S-100 was noted signifying scarcity of interstitial cells and neural elements respectively in these cases. These important findings could mean poor neural activity in the wall of such bladders which will ultimately present as ‘bad bladders’ with poor compliance and impaired growth potential. Such ‘bad bladders’ can in future pave the way for upper tract deterioration as a consequence of a high pressure system. Likewise, continence in such cases is a function of altered bladder dynamics. Anticholinergics are routinely used in bladders with small capacity and high pressures, followed by adjuncts, like clean intermittent catheterization and bladder augmentation in different permutations and combinations, where necessary.

The drug "Oxybutynin hydrochloride" has brought a paradigm shift in the outlook of patients with high pressure, small capacity bladders with a so-called 'normal' wall with a 'normal' muscle layer.\(^10\) The anti-cholinergic action against the M3 muscarinic receptors on the wall of detrusor muscle relaxes it and thereby decreases intravesical pressures and indirectly increases bladder capacity and pharmacologically converts it into an inactive reservoir.\(^11\) However, based upon our observations on the histomorphology in the present study, we believe, that the same will have questionable application.

With increasing knowledge on the surgical management of these cases, survival is approaching 100%;\(^12\) and now the emphasis is shifting on improving the quality of life of these vulnerable children. The above findings lead us to believe that these bladders are, in a way, 'neuropathic' with respect to poor neural innervation and coupled with an inelastic wall constantly pose a threat to the upper tracts.

**Conclusion**

This is the first reported case series of cloacal exstrophy bladder plate histomorphology. We have tried to correlate these with the bladder dynamics and upper tract changes. We hope to further our observations on more specimens and include newer histomorphological parameters in literature to come.

**References**


---

<table>
<thead>
<tr>
<th>Table 1. Comparison of the histological findings of cloacal exstrophy bladder plate with an apparently healthy bladder tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control bladder biopsy</strong></td>
</tr>
<tr>
<td>Mucosa (H-E)</td>
</tr>
<tr>
<td>Submucosa</td>
</tr>
<tr>
<td>Muscle</td>
</tr>
<tr>
<td>Masson's trichrome</td>
</tr>
<tr>
<td>IHC-S-100</td>
</tr>
<tr>
<td>IHC-CD-117</td>
</tr>
<tr>
<td>IHC-SMA</td>
</tr>
</tbody>
</table>


