Journal of Pediatric Urology (2016) 12, 207.e1–207.e5

Congenital renal anomalies in cloacal exstrophy: Is there a difference?

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Keywords
Cloacal exstrophy; Embryology; Renal anomalies; Uterine malformations

Received 6 January 2016
Accepted 22 April 2016
Available online 12 May 2016

Summary

Introduction
Cloacal exstrophy (CE) is the most severe manifestation of the epispadias-exstrophy spectrum. Previous studies have indicated an increased rate of renal anomalies in children with classic bladder exstrophy (CBE). Given the increased severity of the CE defect, it was hypothesized that there would be an even greater incidence among these children.

Objective
The primary objective was to characterize renal anatomy in CE patients. Two secondary objectives were to compare these renal anatomic findings in male and female patients, and female patients with and without Müllerian anomalies.

Study design
An Institutional Review Board-approved retrospective review of 75 patients from an institutional exstrophy database. Data points included: age at analysis, sex, and renal and Müllerian anatomy. Abnormal renal anatomy was defined as a solitary kidney, malrotation, renal ectopia, congenital cysts, duplication, and/or proven obstruction. Abnormal Müllerian anatomy was defined as uterine or vaginal duplication, obstruction, and/or absence.

Results
The Summary Table presents demographic data and renal anomalies. Males were more likely to have renal anomalies. Müllerian anomalies were present in 65.7% of female patients. Girls with abnormal Müllerian anatomy were 10 times more likely to have renal anomalies than those with normal Müllerian anatomy (95% CI 1.1–91.4, $P = 0.027$).

Discussion
Patients with CE had a much higher rate of renal anomalies than that reported for CBE. Males and females with Müllerian anomalies were at greater risk than females with normal uterine structures. Mesonephric and Müllerian duct interaction is required for uterine structures to develop normally. It has been proposed that women with both Müllerian and renal anomalies be classified separately from other uterine malformations on an embryonic basis. In these patients, an absent or dysfunctional mesonephric duct has been implicated as potentially causal. This provided an embryonic explanation for uterine anomalies in female CE patients. There were also clinical implications. Women with renal agenesis and uterine anomalies were more likely to have endometriosis than those with isolated uterine anomalies, but were also more likely to have successful pregnancies. Males may have had an analogous condition with renal agenesis and seminal vesicle cysts. Future research into long-term kidney function in this population, uterine function, and possible male sexual duct malformation is warranted.

Conclusion
Congenital renal anomalies occurred frequently in children with CE. They were more common in boys than in girls. Girls with abnormal Müllerian anatomy were more likely to have anomalous renal development. Mesonephric duct dysfunction may be embyologically responsible for both renal and Müllerian maldevelopment.

Summary Table Results summary.

	Total	Male	Female	*P*-value
N	75	40	35	–
Age at analysis (years ± SE)	18.6 ± 1.3	17.2 ± 1.7	20.1 ± 2.0	0.254
Normal kidneys (*N*, %)	39/75	40.0%	65.7%	0.037
Solitary kidney (*N*, %)	26/75	32.5%	8.6%	0.022
Malrotated kidney (*N*, %)	10/75	15%	11.4%	0.742
Ectopic kidney (*N*, %)	12/75	17.5%	14.3%	0.762
Congenital cysts (*N*, %)	1/75	0%	2.9%	–
Duplicated collecting system (*N*, %)	2/75	2.5%	2.9%	1
UVJ[a] obstruction (*N*, %)	1/75	2.5%	0%	–
Normal Müllerian anatomy (*N*, %)	12/35	n/a	34.3%	–

[a] Ureterovesical junction.

http://dx.doi.org/10.1016/j.jpurol.2016.04.008

Introduction

Cloacal exstrophy (CE) is a rare congenital malformation with abnormalities across organ systems. Like classic bladder exstrophy (CBE), it is a defect of the anterior abdominal wall. In addition to an exstrophied bladder, CE includes gastrointestinal, skeletal, spinal, and genital anomalies. In males, there is separation of the phallic and scrotal halves, and frequent phallic asymmetry. In addition to separated clitoral halves, CE female patients also typically have Müllerian anomalies [1]. Uterus didelphys is the most commonly encountered Müllerian abnormality, however, other anomalies are also encountered, including: vaginal agenesis, mismatched numbers of uteri and vaginas, and obstructed Müllerian outflow [2].

Patients with CBE have been noted to have a higher incidence of congenital renal anomalies (2.8%) than the general population [3]. Likewise, girls with Müllerian anomalies, specifically with hemivagina obstruction, are more likely to experience renal anomalies. Classically, this has been described as the obstructed hemivagina and ipsilateral renal agenesis (OHVIRA) or Herlyn-Werner-Wunderlich syndrome; however, recently, it has been suggested that other anomalies, such as ectopic ureter or renal dysplasia, might also be associated [4].

Given the more extensive abnormalities comprising CE, in the present study it was hypothesize that these patients would have an even greater incidence of renal abnormalities than that seen in CBE. As girls with Müllerian abnormalities may also have an increased risk, it was also hypothesized that the rate of renal abnormalities would differ between male and female patients.

Materials and methods

After obtaining Institutional Review Board approval, a retrospective chart review was performed on patients from a single institution diagnosed with CE. Patients were gathered from an institutionally approved, prospective exstrophy-epispadias-cloacal exstrophy database. Inclusion criteria required patients to have CE and be treated by the Division of Pediatric Urology between January 1974 and July 2013. Patients with classic bladder exstrophy (CBE) or CBE variants were excluded. A total of 112 patients met the study criteria. Of these, complete data were available for 75 patients.

The primary aim of the study was to characterize renal anatomy in patients with CE. The secondary aims were to compare potential anomalies between male and female patients, and between female patients with and without normal Müllerian anatomy. The chart review was performed on clinic notes, radiographic studies and reports, and operative notes. Data points included sex, age at analysis, renal and Müllerian anatomy, and surgery necessitated by renal anomalies. Only congenital renal and uterine anomalies were analyzed in this study. Abnormal renal anatomy was defined as a solitary kidney, malrotation, renal ectopia, congenital cysts, duplication and/or proven obstruction. As ureterovesical junction obstruction could potentially impact care and/or outcomes, this was included as a renal anomaly. Abnormal Müllerian anatomy was defined as uterine or vaginal duplication, obstruction, and/or absence.

The proportion of renal anomalies was calculated and compared with that in the CBE population of Stec et al. [3]. Statistical analysis included Student's *t*-test and two-tailed Fisher's exact probability test. A *P*-value <0.05 was considered statistically significant.

Results

Of the 112 CE patients, 75 had complete data (40 male, 35 female) and were included in the analysis. The mean age at analysis was 18.6 $\pm$ 1.3 years. Renal anomalies were identified in 48% (Summary Table) and included (in order of most to least common): solitary kidney, renal ectopia, malrotation, collecting system duplication, congenital cysts, and ureterovesical junction obstruction.

The proportions of each anomaly are presented in Table 1, where they are also contrasted to CBE [3]. In general, renal anomalies were much more common in CE. The incidence of the most common renal anomaly in CE — solitary kidney — was increased over 30 times that reported in CBE. The most common renal anomaly in CBE — duplicated collecting system — occurred twice as often in CE.

In the present cohort, male patients were more likely than female patients to have any renal anomaly ($P = 0.037$, Fig. 1A); specifically, solitary kidney was more common among male than female patients ($P = 0.022$, Fig. 1B). Of the female patients, 65.7% had at least one Müllerian anomaly (Table 2), which was most commonly duplication of the Müllerian system, either complete (uterus didelphys) or partial, with duplication of either the uterus or vagina. Female patients with renal anomalies were more likely to have abnormal Müllerian anatomy, 47.8% vs 8.3% ($P = 0.027$). There was no difference in the incidence of renal anomalies when comparing male patients to female patients with abnormal Müllerian structures.

Two patients required surgery for a congenital renal anomaly: ureteroureterostomy in a patient with a

Table 1 Comparison of incidence of congenital renal anomalies between cloacal exstrophy and classic bladder exstrophy [1].

Amomaly	Cloacal exstrophy	Classic bladder exstrophy [1]	Increase seen in cloacal exstrophy
Any renal anomaly	1:2	1:36	18.0×
Solitary kidney	1:5	1:154	30.8×
Ectopic kidney	1:6	1:231	38.5×
Duplicated collecting system	1:38	1:77	2.0×