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Prenatal complicated duplex collecting system and ureterocele—Important risk factors for urinary tract infection

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ABSTRACT

Purpose: To evaluate the risk of urinary tract infections (UTIs) in infants with prenatally detected complicated duplex collecting system (CDS) or ureterocele.
Materials and methods: All patients with prenatally detected CDS ($n = 34$) or single system ureterocele ($n = 7$) who were admitted to our institution between 2003 and 2013 were enrolled in this retrospective analysis. Duplex collecting systems with ureterocele ($n = 13$), vesicoureteral reflux (VUR) ($n = 20$) or nonrefluxing megaureter without ureterocele ($n = 7$) were determined as complicated. Twenty-six (63%) patients were females. The prevalence of UTI was compared to 66 controls.
Results: The median follow-up time was 5.5 (1.7–12.2) years. Eighteen (44%) patients and 3 (5%) controls had at least one UTI ($p < 0.001$) at the median age of 0.8 and 0.4 years, respectively ($p = 0.481$). Fifty-seven percent of the UTIs were breakthrough infections and 82% of those were non-*Escherichia coli* infections. UTIs occurred prior to any surgical intervention in 4/13 (31%) patients with ureterocele, in 2/14 (14%) patients with VUR, in 4/7 (57%) patients with both ureterocele and VUR, and in 3/7 (43%) patients with nonrefluxing megaureter without VUR or ureterocele (p-values 0.012, 0.209, 0.001 and 0.010, respectively, compared to controls). Postoperative UTIs were observed in 29% of the girls and in none of the 11 boys ($p = 0.072$). The incidence of UTI after perforation of ureterocele was only 14%.
Conclusions: Children with prenatally detected ureterocele or duplex collecting system associated with nonrefluxing megaureter are at high risk of UTI despite prophylactic antibiotics. In case of prenatally detected ureterocele we suggest to consider early endoscopic perforation.
Level of evidence: III.

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Prenatally detected urinary tract anomalies are relatively common. It has been shown that after 28 weeks of gestation approximately 8% of the fetuses have an abnormal urinary tract ultrasonography finding [1]. Duplication of the collecting system is the most common congenital kidney abnormality. The incidence of duplex collecting system is around 0.7% in normal population [2]. In 5 to 7% of patients with prenatally diagnosed hydronephrosis, the etiology is either duplex collecting system, ureterocele or ectopic ureter [3]. In children with urinary tract infection (UTI) the frequency of duplication is as high as 8% [4,5]. Duplex collecting systems are often complicated with associated pathology: Sixty-nine percent of the complete duplex collecting systems are accompanied by vesicoureteral reflux (VUR) while VUR can be found in 22% of the patients with partial duplex system [4]. The incidence of ureterocele is reportedly around 0.2% [6]. About 80% of infantile ureteroceles occur with duplications and about 60% of these are ectopic. In about 10% of the cases ureterocele is bilateral [7].

Both duplex collecting system and ureterocele are frequently found in children with UTI. However, as far as we know, there are no systematic follow-up studies concerning UTIs in patients with prenatally diagnosed duplex collecting system and ureterocele. In this study we evaluated retrospectively the frequency of UTI in a cohort of children with prenatally detected urinary tract anomaly. We aimed to study 1) the risk and onset of UTIs in children with complicated duplex collecting systems and single or duplex system ureteroceles compared to children with kidney and/or urinary tract abnormality which is not supposed to predispose to UTIs and 2) the impact of surgical

Abbreviations: UTI, urinary tract infection; VUR, vesicoureteral reflux; RUS, Renal ultrasonography; VCUG, voiding cystourethrography; CAP, continuous antibiotic prophylaxis.

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intervention, especially mini-invasive perforation of ureterocele, on the UTI risk in this patient cohort. We hypothesized that well timed operative interventions could reduce the risk of UTIs.

1. Materials and methods

All patients with urinary tract abnormalities (ICD-10: Q60.0–Q64.9 and N13.0–N13.9) diagnosed between January 2003 and December 2013 were identified from the database of the Helsinki University Hospital using electronic search tools. We further selected manually all patients who had prenatally detected urinary tract anomaly. The ethics committee of the Helsinki University Hospital approved the study protocol.

A total of 41 patients (26 girls and 15 boys) with complicated duplex system ($n = 34$) or single system ureterocele ($n = 7$) were identified and included in the study. Duplex collecting systems with upper pole ureterocele ($n = 7$), vesicoureteral reflux (VUR) (lower pole $n = 13$, both poles $n = 1$), upper pole ureterocele and lower pole VUR ($n = 6$) or nonrefluxing megaureter without ureterocele ($n = 7$) were determined as complicated. In four cases with nonrefluxing megaureter without ureterocele ureteral orifice was ectopic. We excluded the patients with duplex system without any additional pathology. Most of the patients had a combination of two or more separate abnormalities, which was taken into account in our analysis.

Duplex system was complete in 32 cases and incomplete in two. Nine patients had bilateral duplex collecting system.

In one case, single system ureterocele was associated with ipsilateral grade 1 VUR and in one case with contralateral renal agenesis. One patient had a single pelvis and two ureters, while the second ureter associated with ureterocele was blind ending.

Thirty-three (80%) patients had postnatal hydronephrosis (pelvic diameter > 10 mm) and in 37 (90%) patients distal ureteral dilatation was diagnosed either from radiological images or clinically during surgery.

None of the male patients was circumcised. Renal ultrasonography (RUS), voiding cystourethrography (VCUG), and renal scintigraphy (MAG3 or DMSA) were performed in all patients. VUR was classified according to the international reflux classification [8]. In the case of bilateral VUR, reflux was graded based on the higher grade.

The control group consisted of 66 age- and sex-matched patients. They all had suspected urinary tract anomaly based on prenatal ultrasonography, but either normal postnatal US or verified urinary tract abnormality supposedly not predisposing to UTI (unilateral renal agenesis ($n = 11$), renal dysplasia or multicystic dysplasia ($n = 37$), single renal or ovarian cyst ($n = 3$), renal or adrenal cystic tumor ($n = 2$), ectopic kidney ($n = 4$) or adrenal hemorrhage ($n = 1$)). All control patients with dysplastic kidneys were evaluated with RUS, VCUG, and scintigraphy to exclude contralateral pathology. The controls' patient records are analyzed until their last visit in either pediatric or pediatric surgical outpatient clinic.

Information about age, gender, antimicrobial prophylaxis, results of imaging studies, and possible operative treatment were collected. Antimicrobial prophylaxis was started in all except one patient with ureterocele and contralateral renal agenesis and it was continued until the urinary tract deformity was successfully treated (for example, with heminephrectomy), or the patient was toilet trained. Occurrence of UTI was collected retrospectively from the patient journals and laboratory database. Bacterial etiology and resistance profile to antibiotics was analyzed. A single bacterial count of 100,000 or more colony forming units (CFU)/mL in voided samples (clean catch urine, urine bag) and any bacterial growth in suprapubic aspiration was considered significant. Bacterial growth in bag sample was confirmed either by suprapubic aspiration or in one case, by puncturing the pyonephrosis. In four patients, the diagnosis was based on two consecutive bag urine samples. In one case with high fever (40 °C), elevated CRP (83 mg/L) and pyuria (10E6/L) UTI was diagnosed based on bacterial growth in only one urine bag sample. In this case, suprapubic aspiration was not successful. Febrile UTI was defined as verified UTI together with fever (>38.5 °C) and/or CRP >35 mg/L [9]. The risk of UTI was calculated in each patient group during the follow-up time at our institution. UTIs after surgery were analyzed separately in patients requiring surgical intervention.

1.1. Statistical analysis

Continuous variables were compared with Mann–Whitney test and categorical variables with Fisher's exact test. We also consulted biostatistician on purpose of multivariate analysis which turned out to be unsuitable for the material. Statistical analyses were done with SPSS statistical package (IBM SPSS statistics 22).

2. Results

2.1. General findings

The median follow-up time for the patients was 5.5 years (range 1.7–12.2 years) and for the controls 3.7 years (range 0.6–10.8 years) ($p = 0.003$). Eighteen (44%) out of the 41 patients and three (5%) out of the 66 controls had UTIs ($p < 0.001$). A vast majority of the first-time UTIs in patients (11/18 (61%)) and all three UTIs in the controls were diagnosed during the first year of life (Fig. 1). VCUG was performed for all of the controls with UTI. The median age during the first UTI was 0.82 years (0.1–7.8 years) in the patients and 0.4 years (0.1–0.8 years) in the controls ($p = 0.481$). UTIs were febrile in seventeen (89%) patients and in one (33%) control patient.

The patients with ureterocele and nonrefluxing megaureter without either ureterocele or VUR had significantly increased risk of UTI ($p = 0.012$ and $p = 0.010$ against controls).

2.2. Infections before operative interventions

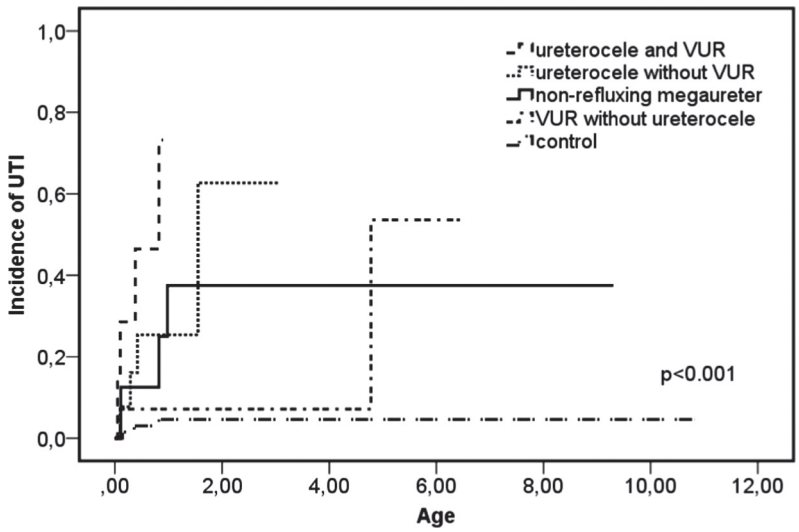
Thirteen (32%) patients ($p < 0.001$ against controls), seven out of the 26 females and six out of the 15 males ($p = 0.492$) had UTI before any operative intervention. The female patients had their first UTI at the median age of 0.2 years (range 0.1–1.0) years and the male patients at the median age of 0.8 (range 0.1–4.8) years ($p = 0.534$).

Patients with ureterocele or nonrefluxing megaureter had significantly more UTIs than the controls (Table 1). Fourteen percent of the patients with VUR but no ureterocele had UTI, which did not differ statistically from controls ($p = 0.209$). On the contrary, patients with ureterocele but no VUR had significantly more UTIs than the controls ($p = 0.012$). The small patient number did not allow reliable analysis of the effect of gender or grade of VUR on the UTI risk in the diagnosis-based subgroups. It was not possible to compare reliably duplex and single system ureteroceles or the impact of VUR in association with ureterocele, either.

Five patients, all of whom had a duplex collecting system, had UTI recurrence before any operative intervention. Two of the five patients with recurrent infections had a second recurrence. One of them had a duplex collecting system with nonrefluxing megaureter and the other had grade 4 reflux and upper pole ureterocele.

2.3. UTI bacteriology and antimicrobial prophylaxis

Altogether 40 patients (98%) were initially on continuous antibiotic prophylaxis (CAP). In 39 cases CAP was started with trimethoprim and in one case with cephalexin. Seventeen out of the 28 (61%) infections occurred during antibiotic prophylaxis. In 13 (76%) cases, the bacteria were resistant to prophylactic antibiotics, in 2 cases the bacteria were sensitive, and in two cases the data about the bacterial resistance was not available. *Escherichia coli* caused 9 (50%) of the 18 first-time



Number of patients at risk						
Age (years)	0.00	2.00	4.00	6.00	8.00	10.00
ureterocele and VUR	*7*	*0*	*0*	*0*	*0*	*0*
ureterocele without VUR	*13*	*1*	*0*	*0*	*0*	*0*
non-refluxing megaureter	*7*	*4*	*2*	*2*	*1*	*0*
VUR without ureterocele	*14*	*6*	*2*	*1*	*0*	*0*
Control	*66*	*56*	*27*	*17*	*5*	*2*

UTI, urinary tract infection; VUR, vesicoureteral reflux

Fig. 1. Incidence of UTI in different patient groups and controls.

infections and 4 (40%) of the 10 recurrent infections in the patients. In the controls, all three infections were caused by *E. coli* ($p = 0.226$).

2.4. VCUG-related infections

A total of 133 VCUGs were performed on patients and controls. In four (3%) cases (three patients and one control), UTI appeared within one week after the investigation. Fifteen percent of the patients' preoperative UTIs and 33% of the controls' UTIs occurred possibly because of VCUG. All of the three patients with VCUG-related UTI had duplex system with dilated ureter. The patients had febrile UTI and the control patient had cystitis. All of the VCUG-related UTIs were first-time UTIs and breakthrough infections. According to our VCUG protocol prophylactic dose of antibiotics is doubled and received for three days from the morning of the examination day.

Table 1
Occurrence of UTIs in different patient groups and controls before any surgical intervention.

	Number of children	Patients with UTI	*p*-Value[a]
Duplex system and nonrefluxing megaureter	7	3	0.010
Duplex system and VUR	14	2	0.209
Ureterocele[b]	13	4	0.012
Single system	7	2	
Double system	6	2	
Ureterocele[b] and VUR	7	4	0.001
Single system	1	1	
Double system	6	3	
Controls	66	3	

Abbreviations: UTI, urinary tract infection; VUR, vesicoureteral reflux.
[a] Incidence of infections against controls.
[b] Single or double system.

2.5. Performed surgical interventions

Thirty-five (85%) patients underwent altogether 41 surgical interventions (Table 2). Median age during the first operation was 1.0 (0.1–3.1) years. Heminephrectomy was performed in 10/13 (77%) patients with duplex system ureterocele. Two of the heminephrectomies were preceded by perforation of the ureterocele. Ureteral neoimplantation was performed in six patients and eight ureteral units because of ureterocele ($n = 3$), gross VUR ($n = 2$), ectopic drainage ($n = 2$) and ureterovesical junction obstruction ($n = 1$). Two ureteric neoimplantations were done for single system associated ureteroceles.

Six patients with VUR were treated operatively. Two patients underwent endoscopic antireflux injection, two patients had unilateral heminephrectomy of the lower pole (both patients also had a contralateral refluxing duplex system), and an additional two patients had ureteral neoimplantation.

According to our protocol heminephrectomy is considered if the renal moiety's function is at most 20% and ureter is removed as far as available. In the late series early puncture of ureterocele became routine while in the early series it was still rare.

Table 2
Number of surgical interventions and operated patients.

Type of surgical intervention	Girls	Boys
Upper pole heminephrectomy	18	5
Lower pole heminephrectomy	0	2
Endoscopic anti-reflux injection[a]	2	0
Ureteral neoimplantation	4	2[b]
Perforation of ureterocele	3	4
Uretero-ureterostomy	1	0
Puncture pyelostomy	0	1
All interventions	28	14
Operated patients	24	11

[a] Deflux®.
[b] In one case, ureteral remnant was dissected and ureterocele perforated as well.

2.6. UTIs in patients with surgical intervention

Seven (20%) of the operated patients experienced UTI after the operation. Five patients had their first UTI after the surgery. The median follow-up time after the latest surgery was 4.5 years (range 0.9–10.8) and the median time from operation to the first UTI was 3.4 (range 1.7–6.9) years. None of the patients with UTI after surgery was on CAP and they had no reoperations, new CAP or UTI recurrences. None of the patients had residual VUR or visible ureteral remnant in renal US at the onset of UTI.

Three out of seven patients had postoperative reflux after perforation of ureterocele (grade 1; $n = 1$, grade 4; $n = 2$). None of them contracted postoperative UTI. Overall, only one patient (14%) had UTI after perforation of ureterocele.

3. Discussion

Data on the incidence of UTIs in children with prenatally diagnosed duplex system with or without ureterocele is scarce. To our knowledge, this is the first long-term analysis about the frequency of UTI in this patient group. According to our findings, ureterocele and nonrefluxing megaureter are significant factors exposing to UTI. The impact of VUR remained controversial. Surgical correction appeared to reduce the risk for UTIs.

Duplex systems are frequently accompanied by other urinary tract abnormalities such as VUR and ureteroceles [4,5]. In our study population with prenatally diagnosed duplex system and significant pathology, 59% of the patients had VUR, 38% had ureterocele, and 21% had nonrefluxing megaureter without ureterocele. Typical findings with the above-mentioned abnormalities were hydronephrosis (pelvic diameter > 10 mm) in 80% and dilated ureter in 90% of the cases. According to previous studies, abnormal DMSA findings are relatively common in patients with duplex system together with other urinary tract abnormalities [4,5]. In our study, there was a poorly functioning kidney pole in over half of the duplex kidneys (data not shown).

In our study, 40% of the patients with ureterocele contracted UTI before any operative intervention. The finding is in line with a previous study where 20% of patients who were selected for perforation of ureterocele at a median age of four months developed UTI before the operation [10]. High-grade VUR together with female gender and duplex system have also been suggested to increase the risk for UTI and renal scarring [11]. In the present study, patients with ureterocele and nonrefluxing megaureter had the highest risk for UTI. Patients with VUR also had increased risk of UTI, but because of our limited number of patients the role of reflux as separate risk factor remains unclear. Gender did not have major influence on the UTI risk in our study population.

The majority (85%) of our patients had one or more operative interventions, heminephrectomy being the most common procedure. According to the previous studies, complete ureterectomy is rarely needed in either upper or lower pole heminephrectomies [12,13]. In our study population, only one patient with ureterocele underwent distal ureteric stump resection after heminephrectomy. Six of the 21 patients with VUR had surgical treatment for reflux. In eight of the 15 unoperated patients, including two cases with grade 4–5 VUR, reflux disappeared without any operative intervention. Our present results support the previous findings suggesting that low grade VUR, even in association with duplex collecting system, is of minor clinical importance and tends to heal without specific treatment [11].

Thirty-two percent of the patients experienced at least one UTI without or before any operative intervention. One fifth of these patients experienced UTI recurrence later despite successful operation. Nineteen percent of the operated patients had UTI after successful surgery, and 70% of these infections were first-time UTIs. None of these patients had UTI recurrences or need for further urological procedures. All the patients who had infections after surgery were girls, which supports the previous findings showing that febrile UTIs are relatively uncommon in males after effective surgical decompression of the urinary tract [14]. In our population, the risk of UTI was 14% after mini-invasive perforation of ureterocele and 22% after upper pole heminephrectomy. In a previous study, 23% of the patients who had postnatally diagnosed ureterocele and none of the patients who were prenatally diagnosed got UTI after endoscopic puncture of ureterocele [10].

Children with antenatally diagnosed hydronephrosis and high grade VUR, obstructed ureterovesical junction, or dilated ureter are observed to be at increased risk of UTI. CAP seemed to reduce the risk for UTI [15]. In our study, 61% of the first-time UTIs and 60% of the UTI recurrences were breakthrough infections. Only 18% of them were caused by *E. coli*. On the contrary, 91% of the UTIs that occurred in patients without CAP were caused by *E. coli*, and all of these bacteria were sensitive to the antibiotics tested. Although CAP apparently reduces the number of UTIs it increases the risk of infections caused by resistant bacteria.

The main limitation of our study lies in the size and diversity of our patient material. Therefore we were not able to divide our study population into diagnosis-based subgroups and analyze the risk of UTI in various combinations of abnormalities. Another caveat is that the study was performed retrospectively, which is why urine sample acquisition was not done in a wholly uniform manner. UTIs were diagnosed by either suprapubic aspiration, clean catch urine sample, or in some cases, urine bag samples. Since the majority of our patients were operated on in early childhood to prevent UTIs our results do not represent pure natural history of the malformations.

There are also several strengths in the present study. All patients were carefully followed up in our unit and all radiological imaging studies were performed in an experienced pediatric radiological unit. The information about the medical history, imaging studies, and laboratory test results was meticulously recorded. We explored the data manually and read all the information considering the targets of this study. All UTI episodes were analyzed to ensure that there were no discrepancies between the clinical and laboratory findings.

4. Conclusions

We conclude that children with ureterocele and duplex system with severe nonrefluxing megaureter are at high risk of UTI despite the antibiotic prophylaxis. While infections after successful operations remain rare, mini-invasive ureterocele perforation should be considered at young age to reduce UTIs. CAP may predispose the patients to resistant non-*E. coli* infections.

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