POSITIVE FEEDBACK LOOP FOR CYSTITIS CYSTICA: THE EFFECT OF RECURRENT URINARY TRACT INFECTION ON THE NUMBER OF BLADDER WALL MUCOSA NODULES

Kristina Vrljičak[1], Daniel Turudić[2], Ivan Bambir[2], Ivan Pavao Gradiški[2], Borislav Spajić[3], Danica Batinić[1], Marija Topalović-Grković[4], Marija Spajić[5], Danko Batinić[1] and Danko Milošević[1]

[1]Department of Nephrology, Dialysis and Transplantation, Zagreb University Hospital Center, [2]University of Zagreb School of Medicine; [3]Department of Urology, Sestre milosrdnice University Hospital Center; [4]Department of Anesthesiology and Intensive Care, Zagreb University Hospital Center, Zagreb; [5]Department of Pediatrics, Karlovac General Hospital, Karlovac, Croatia

SUMMARY – The main purpose of this study was to demonstrate positive feedback loop between bladder wall nodules (nodules being one of the key diagnostic factors), bladder wall thickness, and recurrent urinary tract infections. Cystitis cystica was diagnosed in 115 prepubertal girls (mean age 7.79±3.05 years) by optic examination of bladder mucosal nodules and by ultrasonographic measurement of bladder wall thickness. Bladder wall thickness increased with the frequency of recurrent urinary tract infections as well as with the number of nodules on bladder wall mucosa (3.52±0.522 mm ≤5 nodules *vs.* 4.42±0.429 mm 6-10 nodules *vs.* 5.20±0.610 mm >10 nodules, respectively). Study results suggested that early control of urinary tract infections by chemoprophylaxis could prevent higher grades of bladder wall mucosal changes and consequently shorten the length of chemoprophylaxis.

Key words: *Cystitis – pathology; Urinary tract infections – complications; Mucous membrane – ultrasonography; Recurrence*

Introduction

Cystitis cystica (CC) is a clinical entity that can occur at any age. It is caused by repeated urinary tract infections and is characterized by nodular bladder mucosal changes[1-8]. In children, the most common age and gender for CC are prepubertal girls and its presence causes numerous recurrent urinary tract infections (UTI)[6]. It may but need not be accompanied by various preexisting anomalies of the urinary tract (such as vesicoureteral reflux)[1,3,5]. The diagnosis of CC was somehow neglected in the past decades as endoscopy procedure (a golden standard) for diagnosis and proper staging of CC was understandably avoided as much as possible. We believe that recurrent UTIs *per se* can cause CC formation and creating positive feedback loop consequently enhances the number of nodules on bladder wall mucosa. Therefore, we conducted the present study to confirm the aforesaid statement.

Correspondence to: *Danko Milošević, MD, PhD*, Zagreb University Hospital Center, University of Zagreb School of Medicine, Department of Nephrology, Dialysis and Transplantation, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: danko.milosevic@zg.t-com.hr

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Patients and Methods

A total of 115 prepubertal girls with CC were examined. All patients had recurrent UTIs and were treated with antibiotics for a long time with no obvious

explanations. Children with urinary tract anomalies were excluded from the study as well as children with acute UTI and major bladder anomalies (diverticula, fistulae in neighboring organs, ureterocele, neurogenic bladder, or posterior urethral valve). Kidney and urinary tract ultrasound (US), voiding cystourethrography (MCUG) and in doubt of possible renal scarring radionuclide scan (DMSA) were performed. The instrument used on cystoscopy was Olympus Ch 8-13. An informed consent was obtained from the parents and legal guardians before endoscopic procedure.

Endoscopy was performed using Olympus (Ch 8-13) instruments according to the individual patient's age. Careful examination of the meatus and perineum was performed before the procedure. The meatus and cystoscope were disinfected and lubricated according to the procedure previously described[6-8]. Locoregional and general anesthesia was applied. The bladder was thoroughly emptied before examination and subsequently filled with a precisely defined volume of sterile water warmed to body temperature (37 °C), taking into account the expected bladder capacity for each age group[8,9]. Cystoscopy was performed mostly as an outpatient procedure.

Endoscopic presence of multiple, small, round, raised areas of pearl, brown or yellowish nodules on the mucous membrane of the urinary bladder was considered as CC positive[1,4]. Nodular changes were categorized as incipient (group A, up to 5 nodules, 30 girls); mild (group B, 6-10 nodules, 27 girls), and moderate to severe (group C, more than 10 nodules, 24 girls)[8].

Immediately after cystoscopy, the US bladder wall thickness (BWT) was measured in a standard transverse and sagittal position using convex 3.5 to 7 MHz probes (groups A, B and C). The lateral bladder wall was measured in transverse view, while the posterior wall in the thickest point was recorded in sagittal view. Normal mucosal BWT was obtained by US examination in CC free prepubertal girls (n=34)[8].

The data obtained were expressed as numbers and percentages. Measured data were expressed as arithmetic mean and standard deviation (SD). Data were processed by the analysis of variance (two-way ANOVA) and Tukey HSD post hoc test with correction for unequal sample sizes. The level of statistical significance was set at $p \leq 0.05$[10].

Results

The study included 115 prepubertal girls, median age 7.79 ±3.05 years (arithmetic mean ± SD). BWT measurement showed different values for each group of children: group A: 3.52±0.522 mm; group B: 4.42±0.429 mm; group C: 5.20±0.610 mm; and control group: 2.64±0.679 mm. Analysis of variance yielded a statistically significant difference among all study groups ($p<0.001$) and Tukey HSD test proved their dissimilarity from each other. Differences among all groups were statistically significant ($p \leq 0.05$) (Table 1). The interdependence among groups A, B, C and control group of healthy children in BWT measurement is graphically illustrated in Figure 1. Each square represents certain group (healthy children and children with different number of nodules). BWT increased progressively with the grade of nodules *per* group. Therefore, the US BWT measurement showed positive correlation with the increasing number of bladder wall mucosal nodules.

A relation was presumed between UTI frequency and increased number of nodules for each consecutive group. Therefore, the number of UTIs/year was compared among groups A (1-5), B (6-10) and C (>10) nodules. Group A had predominantly 2 UTIs (35.09%), clearly distinctive from group B (3 UTIs, 28.57%). Group C had a similar percentage of 3 UTIs (26.79%) as group B, but comparably higher percentage of ≥4 UTIs. Consequently, all groups of children

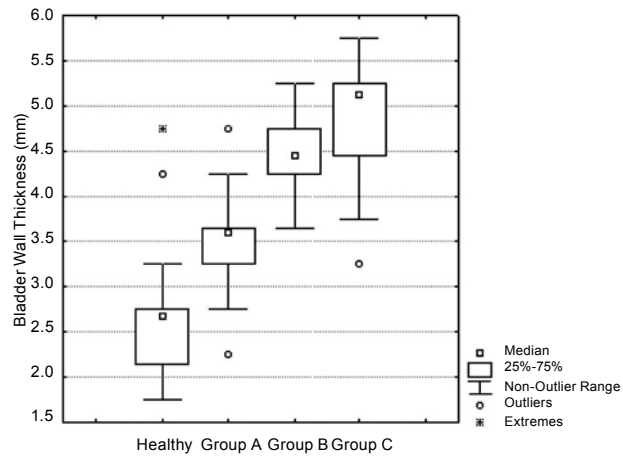

Fig. 1. Comparison of nodule number determined by endoscopy (groups A, B and C) and bladder wall thickness measurement.

Table 1. Multiple comparisons of healthy children and children with different number of nodules (A 1-5; B 6-10; C >10) performed by analysis of variance (two-way ANOVA) and Tukey HSD post hoc test with correction for unequal sample sizes

Group	Healthy	A 1-5 nodules, 30 girls	B 6-10 nodules, 27 girls	C >10 nodules, 24 girls
Healthy		<0.001	<0.001	<0.001
A	<0.001		<0.001	<0.001
B	<0.001	<0.001		0.048
C	<0.001	<0.001	0.048	

Differences among all groups were statistically significant (p≤0.05)

had different mean numbers of UTIs (mean ± SD). The mean number of UTIs increased with the number of mucosal nodules. Gradual increase in the number of UTIs with the number of bladder wall mucosal nodules is shown in Table 2. Their interdependence was tested by multiple comparison using analysis of variance (two-way ANOVA) (p<0.001) and Tukey HSD post hoc test with correction for unequal sample sizes. Statistically significant differences (p≤0.01) in the number of UTIs were found for all study groups (A, B and C). Therefore, group A showed difference *vs*. groups B and C; group B *vs*. groups A and C; and group C *vs*. groups A and B (p<0.001 all).

Discussion and Conclusion

It was presumed that frequent UTIs trigger local immunoreactions creating positive feedback loop on the spread of bladder mucosa CC[3]. It was determined by endoscopy and confirmed by US BWT measurement to prove dissimilarities among all groups of children (Table 1). US BWT measurement is the primary noninvasive diagnostic indicator of CC[8]. As the grade of nodule number increased, so did BWT (mm) (Fig. 1). Differences in nodule number among the groups are clearly depicted, thus pointing to US BWT measurement as a reliable diagnostic tool for CC staging.

This diagnostic criterion was then compared with the number of UTIs/year to determine their potential relationship. Table 2 shows differences among all groups of prepubertal girls, while multiple comparisons for UTIs of groups A, B and C performed by the analysis of variance and Tukey HSD post hoc test confirmed its positive interdependence. The more frequently acute UTIs/year are treated by medication, it is more likely that a greater number of bladder wall mucosa nodules are present. We know from previous reports that a greater number of nodules means

Table 2. Incidence of urinary tract infections/year per nodule number (groups A, B and C)

Number of UTI/year	Group A* n (%)	Group B* n (%)	Group C* n (%)
<2	82 (23.98)	32 (9.9)	19 (5.6)
2	120 (35.09)	91 (28.26)	53 (15.7)
3	81 (23.68)	92 (28.57)	90 (26.79)
4	22 (6.43)	54 (16.77)	83 (24.70)
>4	20 (6.14)	38 (13.70)	59 (22.75)
Missing	16 (4.68)	9 (2.80)	15 (4.46)
Mean ± SD	2.5±1.5	3.0±1.8	4.0±2.3

*Total number and percentage of urinary tract infections (UTI)

prolonged chemoprophylactic treatment with more questionable and difficult compliance[6,7]. It is therefore essential to diagnose CC as early as possible before it progresses to higher stages. A reduction of UTI/s *per* year is the best prevention of this undesirable progression[4,7]. It seems plausible not to treat recurrent UTIs just as they naturally occur, but to administer chemoprophylaxis at due time for their prevention. Early prevention of higher grade CC will certainly improve the future child's quality of life while at the same time avoiding uroprophylactic/antibiotic contact with bacterial flora as much as possible.

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Sažetak

POZITIVNA POVRATNA SPREGA CISTIČNOG CISTITISA: ULOGA POVRATNIH INFEKCIJA MOKRAĆNOG SUSTAVA U BROJU NODOZNIH ČVORIĆA U SLUZNICI MOKRAĆNOG MJEHURA

K. Vrljičak, D. Turudić, I. Bambir, I. P. Gradiški, B. Spajić, D. Batinić, M. Topalović-Grković, M. Spajić, D. Batinić i *D. Milošević*

Osnovni cilj ove studije bio je prikazati pozitivnu povratnu spregu između broja nodula na sluznici mokraćnog mjehura (ključni čimbenik u dijagnozi), debljine sluznice mokraćnog mjehura i broja ponavljanih infekcija mokraćnog sustava. U 115 djevojčica srednje predpubertetske dobi od 7,79±3,05 godina dijagnoza cističnog cistitisa je postavljena cistoskopskim pregledom sluznice mokraćnog mjehura i ultrazvučnim mjerenjem njezine debljine. Debljina sluznice se progresivno povećavala s brojem nodula (3,52±0,522 mm ≤5 nodula prema 4.42±0.429 mm 6-10 nodula prema 5,20±0,610 mm >10 nodula) usporedno s povećenjem broja uroinfekcija. Smatramo da se ranom profilaksom uroinfekcija može spriječiti razvoj opsežnih promjena na sluznici mokraćnog mjehura s posljedičnim skraćenjem profilaktične primjene antibiotika/uroantiseptika.

Ključne riječi: *Cistični cistitis – patologija; Mokraćni sustav, infekcije – komplikacije; Sluznica – ultrazvuk; Recidiv*