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Cystitis Cystica and Recurrent Urinary Tract Infections in Children

Danko Milošević[1], Danica Batinić[1], Goran Tešović[2], Paško Konjevoda[3], Hrvoje Kniewald[1], Mirna Šubat-Dežulović[4], Lana Grković[1], Marija Topalović-Grković[1], Daniel Turudić[1] and Borislav Spajić[5]

[1] Department of Pediatrics, Zagreb University Hospital Center, Zagreb, Croatia
[2] Department of Pediatric Infectious Diseases, School of Medicine, Zagreb University, Zagreb, Croatia
[3] »Ruđer Bošković« Institute, Zagreb, Croatia
[4] Department of Pediatrics, Rijeka University Hospital Center, Rijeka, Croatia
[5] Department of Urology, »Sestre milosrdnice« University Hospital, Zagreb, Croatia

A B S T R A C T

The pathogenesis of recurrent urinary tract infections (UTIs) in preschool children with anatomically correct urinary tract (UT) is rather obscure. In girls, the bladder wall changes of cystitis cystica (CC) may be per se responsible for UTIs recurrence. During the 20-year period, 127 preschool children (125 girls; median age: 6.1 years) with CC, in whom UT anomalies were excluded, were diagnosed. The mean duration of UTIs symptoms prior to diagnosis was 3.31±2.51 years. Cystoscopical findings were labelled as mild, moderate and severe in 22.8%, 39.4% and 37.8% of patients, respectively. Following the confirmation of CC, long-term chemoprophylaxis with sulfamethoxazole-trimethoprim/nitrofurantoin was administered. A one year UTI-free period after chemoprophylaxis discontinuation was defined as therapeutic success. With 2.5 years median duration of regular chemoprophylaxis this goal was achieved in 58 children mainly with mild/moderate CC. Thirty children from »improved/unchanged« group taking regular prophylaxis had significant reduction of UTIs (»improved«). Only 12 children belonging to the same group taking regular prophylaxis and all children with irregular prophylaxis had approximately the same number of UTIs as before treatment (»unchanged«). The »improved/unchanged« outcomes were predominantly found in children with severe form of CC. Although urodynamic disturbances detected in more than 50% of patients in whom urodynamics was performed were not found influential on the disease outcome, they could be responsible for its development. The results of our study suggest that regular and long-lasting chemoprophylaxis remains a basis for successful treatment for majority of patients with CC, even those with severe forms. If not treated properly with chemoprophylactic agents and without fair compliance in taking drugs, the disease is prone to recurrent UTIs.

Key words: *cystitis cystica, children, recurrent urinary tract infections, uroprophylaxis, urodynamic disturbances, bladder wall*

Introduction

Cystitis cystica (CC) represents a clinical entity characterized by nodular changes of bladder mucosa protruding into the vesical lumen in the form of pearl, pink, brown or yellowish cysts[1]. The cysts are usually found in the trigonum region, the bladder neck and around ureterovesical junction although rarely they can be detected in the ureters as well as in the renal pelvis[1–6]. Histologically, cysts are composed of lymphoid aggregates in lamina propria[2,3]. The pathogenesis of the disease is not entirely clarified although it is believed that CC represents local immune response to a chronic inflammatory stimulus[3,4].

CC can be detected even in early infancy although the usual age at diagnosis is between four and 10 years[1]. In all previously published studies almost all patients with CC were girls[1,3–7]. In children with CC the common symptoms of disease are dysuria, frequency, macrohematuria, urgency, incontinence, secondary enuresis and unpleasant urine odour[1,4]. Although CC could be found

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in up to 1/3 of patients with vesicoureteral reflux as well as in children with other urinary tract (UT) anomalies, it can also be diagnosed in subjects with anatomically correct UT[1,4,5,7]. In almost half of children with CC various urodynamic abnormalities, mainly bladder instability and detrusor-sphincter dysinergy, can be diagnosed as well[8,9].

The relationship of CC and urinary tract infection (UTI) is well established and antimicrobial prophylaxis is usually recommended to those patients[1,3,5,7–9].

The majority of rather scarce reports on CC date from the 20th century[1–9]. The reason for this scarcity lies probably in the fact that the diagnosis of CC until recently depended exclusively on invasive diagnostic procedure, i.e. cystoscopy, which has to be avoided in children as much as possible[10].

In this study we present the results of a retrospective analysis of our patients with cystoscopically confirmed CC. The aim of the study was to investigate the relationship of disease outcome to age at the diagnosis of CC, duration of period of UTI recurrence prior to establishing the diagnosis, severity of cystoscopic findings, urodynamic findings and compliance (adherence) to UTI chemoprophylaxis. In order to avoid another invasive procedure, we choose not to perform a secondary cystoscopy and to rely on clinical course alone.

Patients and Methods

A retrospective multicenter study that covered the 20-year period (January 1st, 1986–December 31st, 2005) was performed. Data on sex, age, period of UTIs recurrence before establishing the diagnosis of CC, cystoscopic findings, urodynamic findings, as well as on compliance (adherence) to UTI prophylaxis and its duration were obtained from medical history records.

The most frequent indications for cystoscopy were: suspicion of UT (presumably bladder) anomalies and frequent recurrences of UTIs occurring without obvious explanation. Only children in whom UT anomalies were definitely excluded were subjects for further analysis.

Endoscopy was performed using Olympus (Ch 8–13) instruments according to the individual patient's age. An informed consent was obtained from patients´ parents prior to cystoscopy. Careful examination of the meatus and perineum was performed before the procedure. The meatus and cystoscope were disinfected and lubricated due to procedure previously described[11]. Locoregional and general anesthesia was applied. The bladder was thoroughly emptied before examination and subsequently filled with a precisely defined volume of sterile water heated to body temperature (37°C) taking into account the expected bladder capacity for each age group. Cystoscopy was performed mostly as an outpatient procedure. Cystoscopic presence of multiple, small, round, raised areas of pearl, brown or yellowish coloration on the bladder mucosa was considered as a positive diagnosis[1,3,4]. The number of nodular changes were categorized as incipient (group A, up to 5 nodules), mild (group B, 6–10 nodules) and moderate to severe (group C>10 nodules). After the procedure termination, a 3-day antibiotic prophylaxis was administered to patients with negative cystoscopic finding, while in patients with confirmed diagnosis of CC a long-lasting chemoprophylaxis with sulfamethoxazole-trimethoprim or nitrofurantoin was initiated. The urine culture was performed on a monthly basis. After at least one year of therapy, the chemoprophylaxis was discontinued for the first time in all children with continuously sterile urine. For children with at least one significant bacteriuria finding or one breakthrough UTI episode during the first year of follow-up, the prophylaxis was recommended for further 12 months. After 2 years the check-up of prophylaxis discontinuation was performed every 6 months. Adherence to chemoprophylaxis was estimated according to parental statements. The group of children taking prophylaxis according to our recommendations were labelled as »compliant« while children who didn't take prophylaxis regularly comprised the »non-compliant« group. The disease outcome was labelled as (i) cured, (ii) improved/ unchanged. Children with at least one-year UTI-free period after antimicrobial prophylaxis discontinuation were considered as being successfully treated (»cured«). The term »improved/unchanged« describes children with reduced or unchanged incidence of UTI compared to the period prior to establishing the diagnosis of CC.

Urodynamic investigation consisted of simultaneous measuring and recording of bladder and abdominal pressure, both during filling and voiding. Urine flow rate and sphincter electromyography (pressure-flow-EMG study) was performed according to procedure previously described[8]. The urodynamic examinations were carried out with a DISA 2100 URO-System. Urodynamic findings were classified according to International Children´s Continence Society (ICCS) terminology[12].

Categorical non-ordered data were compared using χ^2-test or Fisher exact-test. For the comparison of groups with ordered data the Jonckeere-Terpstra or Mann-Whitney test were used. All tests were two-sided. The level of statistical significance was set at $p \leq 0.05$. The SAS statistical computer package (version 9.1.3, SAS Institute Inc, Cary, NC, USA) was used for all analyses.

Results

One hundred and twenty seven patients with confirmed diagnosis of CC and no concomitant UT anomalies were included in the study. All patients, except two, were females. The median age at diagnosis was 6.1 years (range: 4.3–8.2 years) with mean duration of symptoms (recurrent UTIs) prior to diagnosis 3.31±2.51 years. All children received uroprophylaxis in the mean duration of 2.7±2.07 years. In the group of »cured« children (58 patients, 45.7%) prophylaxis lasted for 2.8±2.3 years, while in the »improved/unchanged« group (69 patients, 54.3%) the children have taken chemopropylaxis for 3.6±2.6 years. However in both groups of patients the median

TABLE 1
THE DISEASE OUTCOME IN RELATION TO AGE AT DIAGNOSIS, DURATION AND ADHERENCE TO UTI PROPHYLAXIS

	»Cured«	»Improved/unchanged«	p-value
Age at diagnosis, yrs (median; range)	6.1; 4.3–8.2	6.5; 4.7–7.8	NS
Duration of chemoprophylaxis, yrs (mean±st. dev.)	2.8±2.3	3.6±2.6	NS
Number of patients taking prophylaxis regularly (%)	58 (100%)	42 (60.8%)	<0.0001

NS – non-significant

TABLE 2
THE DISEASE OUTCOME IN RELATION TO CYSTOSCOPIC FINDING

Outcome	Group A (%)	Group B (%)	Group C (%)	Total (%)
»Cured«	17 (13.4)	26 (20.5)	15 (11.8)	58 (45.7)
»Improved/unchanged«	12 (9.4)	24 (18.9)	33 (26.0)	69 (54.3)
Total	29 (22.8)	40 (39.4)	48 (37.8)	127 (100.0)

Group A: ≤ 5 nodules, Group B: 6–10 nodules, Group C: >10 nodules; χ^2=16.802; df=4; p=0.002

TABLE 3
URODYNAMIC FINDINGS IN DIFFERENT OUTCOME GROUPS OF PATIENTS WITH CC

Outcome	Normal findings (%)	Pathological findings* (%)	Total (%)
Cured	10 (18.9)	11 (20.8)	21 (39.7)
Improved/Unchanged	12 (22.6)	20 (37.7)	32 (60.3)
Total (%)	22 (41.5)	31 (58.5)	53 (100.0)

*overactive bladder, dysfunctional voiding; χ^2=non significant difference between groups (p=0.738)

duration of chemoprophylaxis was 2.5 years. All cured children (58/58) had taken prophylaxis regularly, alongside with 42 out of 69 patients in »improved/unchanged« group (Table 1). Twenty seven patients have taken prophylaxis irregularly. All belong to »improved/unchanged« group. Comparing two outcome groups no statistically significant differences were found in age at establishing the diagnosis or in total duration of chemoprophylaxis, while the outcome of the disease showed close relationship with compliance to UTI prophylaxis (Table 1). In »improved/unchanged« group, among patients who have taken prophylaxis regularly two subgroups of patients could be distinguished; a major one (30 patients) who »improved« on prophylaxis and a minor (12 children) in whom prophylaxis seemed to be non-beneficial. In comparison of disease outcome with severity of cystoscopic finding statistically significant differences were also found. The majority of children belonging to »cured« group had only mild to moderate cystoscopic findings (groups A and B), while in »improved/unchanged« group, almost half of them (33 patients, 47.8%) had severe form of disease (Table 2). Urodynamic examination was performed in 53 children, of whom in 31 (58.5%) overactive bladder and/or dysfunctional voiding were diagnosed. Although, a considerable number of pathological urodynamic patterns were found, no statistically significant differences were noticed comparing patients from different outcome groups (Table 3).

Discussion

One hundred and fifty years after the first description of CC, there is still much controversy regarding this condition[2]. Although in all previously published studies recurrent infections are proposed as the main contributing factor in pathogenesis of CC in childhood, the real biology of this condition remains unresolved[1,3–5,7]. The major reason for accepting the »infectious hypothesis« as a key factor in development of CC is empirically based, namely CC do not emerge in children without previous history of recurrent UTIs[1,3]. The additional proof supporting connection of long-lasting infection and CC is the beneficial role of eradication of bacteriuria in these patients[3,7,9]. However, the fact that practically all patients with CC are females, emphasizes the potential role of other yet undefined factors in development of the disease. Although unknown influential factors in the pathogenesis and clinics of CC still exist, scientists and clinicians showed curious lack of interest in this condition in the last few decades. Only two clinically oriented articles in peer reviewed journals dealing with CC were published in the last twenty years[4,10].

In our study we selected only children with anatomically correct UT in order to perceive CC as an independent entity and to exclude possible additional impact of UT anomalies on recurrent UTIs occurrence.

The majority of our patients were preschool age girls with a history of recurrent UTIs period of approximatelly 3 years prior to cystoscopically established diagnosis of CC. Thence, according to our experience, as well as data published previously, in patients with long-lasting history of UTIs recurrence without obvious explanation, the diagnosis of CC should be considered[3–5]. However, due to a reasonable common practice of avoiding cystoscopy, this diagnosis remains unrecognized in the majority of children with anatomically correct urinary tract thus underestimating its role as a cause of recurrent UTIs in young girls. In the future, ultrasound bladder wall thickness measurement as a surrogate method for diagnosing of CC could resolve this problem, although, judging on available results, further investigations on ultrasound applicability in this indication are needed[10].

The outcome of CC in our patients showed close relation to the severity of the disease, contrary to previous reports[4]. A favorable outcome of CC occurred mostly in children with mild to moderate cystoscopic changes, and *vice versa*, the »improved/unchanged« outcomes were found predominantly in children with more severe form of CC. This fact enables us to conclude that the intensity of local finding could serve as a prognostic factor in evolution of the disease.

Urodynamic examination revealed a high rate of lower UT dysfunction among our patients with CC, emphasizing the possible causal relationship of urodynamic disturbances to development of CC, or inversely a possible influence of CC on development of urodynamic disturbances. However, according to our data, the existence of urodynamic abnormalities was not found as a factor influencing the outcome.

The ultimate goal for all clinicians is to cure their patients. That was the main reason why we decided to concentrate our efforts on distinguishing the »cured« group of patients from »improved/unchanged« group. However, it has to be emphasized that the »improved/unchanged« group included 42/69 children receiving UTI prophylaxis regularly who did not get »cured«. Therefore, we may assume that UTI prophylaxis is somewhat questionable in the eradication of CC. But if we closely examine »improved/unchanged« group it becomes clear that this group comprises of two subgroups of patients; a major one with children who »improved« on prophylaxis and a minor (12/34 children with »unchanged« CC) in whom prophylaxis not seemed to be beneficial. The majority of children in the first subgroup had good compliance and they benefited from chemoprophylaxis judging by a decrease in the number of UTIs. The second subgroup merely consisted of noncomplient children, taking chemoprophylaxis irregularly or not at all, with unchanged UTI recurrence compared to the period prior to diagnosis of CC.

The real impact of CC in children with recurrent UTI poses a puzzle to pediatricians regarding the duration of antibiotic chemoprophylaxis. We are aware that it is difficult to determine the exact time of CC disappearance without repeated cystoscopy, and thus the optimal duration of antibiotic chemoprophylaxis. In resolving this dilemma our results could be combined with the conclusions reported previuosly[1,3,5]. Our personal experience further corroborated by results presented here encourage us to conclude that long-lasting (i. e. 2,5 years) regular UTI chemoprophylaxis proves most beneficial in successful treatment of children with CC. Similar period of chemprophylaxis proved beneficiary for the most of our »improved« subgroup of children. As long term use of nitrofurantoin and sulfamethoxazole-trimethoprim is required, close monitoring of adverse reactions as well as bacterial flora resistance is needed. In concordance with experience published recently, we also did not find serious adverse reactions of long term use of UTI prophylaxis[14]. Although wishing to explore the CC as an independent clinical entity, children with concomitant UT anomalies were excluded from analysis, the presence of CC in anatomically abnormal UT is a well known fact established by previous studies[1,4,5]. In such situations, especially among children with vesicoureteral reflux (VUR), the resolvement of VUR does not automatically means the reduction of UTIs recurrence. The consequent conclusion is that in all children with VUR in whom UTIs persist after the VUR resolvement, CC should be considered as a possible cause.

Conclusions

The recurrence of UTIs in preschool aged girls with anatomically correct UT is closely related to the presence of CC. In the absence of proper noninvasive diagnostic technique that can confirm the diagnosis, the importance of CC and recurrent UTIs coexistence is underestimated due to rarely performed cystoscopy. Although urodynamic disturbances could be at least partly responsible for the development and duration of CC, they can be found in patients without dysfunctional voiding, too. Long-term chemoprophylaxis with good compliance is closely related to a favorable disease outcome and a fair chance of full recovery.

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D. Milošević

Department of Pediatrics, Zagreb University Hospital Center, Kišpatićeva 12, 10000 Zagreb, Croatia
e-mail: danko.milosevic@zg.t-com.hr

CISTIČNI CISTITIS I OPETOVANE INFEKCIJE MOKRAĆNOG SUSTAVA U DJECE

S A Ž E T A K

Uzrok ponavljanja infekcije mokraćnog sustava (IMS) u značajnog broja predškolske djece s anatomski normalnim urotraktom (UT) ostaje nerazjašnjen. U neke od ove djece, promjene sluznice mokraćnog mjehura koje nazivamo cistični cistitis (CC) mogu *per se* biti odgovorne za opetovanje IMS. Tijekom 20 godina CC smo dijagnosticirali u 127 predškolske djece urednog UT (djevojčice (125/127; medijan dobi: 6.1 godina). Trajanje rekurentnih IMS prije postavljanja dijagnoze CC iznosilo je prosječno 3,31±2,51 godine. Cistoskopski nalaz kategoriziran je kao blagi, umjereni i obilan (u 22,8%, 39,4%, odnosno 37,8% bolesnika). Nakon postavljanja dijagnoze u svih je bolesnika započeta kemoprofilaksa sulfametoksazol-trimetoprimom/nitrofurantoinom. Terapijski uspjeh definirali smo razdobljem od godinu dana bez pojave recidiva IMS nakon ukidanja kemoprofilakse, a postignut je u 58 djece s uglavnom blagim i umjerenim oblikom CC. Trajanje profilakse IMS prije postignutog izlječenja, iznosilo je 2,5 godine (medijan). Povoljan učinak redovitog uzimanja kemoprofilakse uočen je i u djece u koje izlječenje nije postignuto. U djece, s uglavnom obilnim nalazom CC (30/42), uočeno je smanjenje broja IMS (»poboljšani«), dok se u njih 12, broj IMS nije smanjio (»nepromijenjeni«). U svih 27 djece u kojih se profilaksa provodila neredovito, nije došlo do promjene broja recidiva IMS. Urodinamske promjene nađene su u više od polovice djece s CC u kojih je urodinamsko ispitivanje provedeno. Premda nije dokazan, barem djelomičan doprinos patoloških urodinamskih promjena u nastanku i podržavanju cističnog cistitisa, može se pretpostaviti. Na osnovu naših rezultata, zaključujemo kako je redovita kemoprofilaksa IMS u djevojčica s CC i anatomski normalnim UT osnovni preduvjet za njihovo sprječavanje. Neprovođenje redovite kemoprofilakse uzrokuje učestalo ponavljanje IMS u ove djece.