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Original Article

Urinary tract infections in children with myelodysplasia in whom clean intermittent catheterization was administered

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Abstract

Aim: In this study, it was aimed to evaluate the frequency of significant bacteriuria and antibiotic resistance characteristics in children with myelodysplasia in whom clean intermittent catheterization was administered.

Material and Methods: The study group was composed of 71 patients with myelodysplasia who were found to have significant bacteriuria (age: 8.20±4.57 years; 39 girls) and the control groups was composed of 49 children who were diagnosed with community-acquired urinary tract infection (age: 7.94±4.17 years; 29 girls). The patient and control groups were evaluated in terms of the microorganisms grown in urinary cultures and antibiotic resistance characteristics. The study approved by the ethics committe (14/02/2012-19/E).

Results: Growth of *Escherichia coli* (*E. coli*) was found with the highest rate in myelodysplasic patients. However, when compared with the control group in terms of microorganism types, an increase in the growth rates of the microorganisms excluding E. coli was observed in the patients with myelodysplasia which was close to the significance limit (p=0.055). When antibiotic resistance properties were examined, a significantly increased resistance against co-trimaxazole was found in the patient group compared to the control group (p=0.001). 84.5% of the patients were using prophylactic antibiotic including mainly co-trimoxazole. A significantly increased co-trimoxazole resistance was also found in the patients who were using prophylactic antibiotic compared to the patients who were not using prophylactic antibiotic (p=0.025). The rate of symptomatic UTI was found to be 21% in the patients with myelodysplasia and a significant increase was found in the complaints of abdominal/side pain and nausea/vomiting as well as fever in these patients compared to the patients with asymptomatic bacteriuria (p=0.029 and p=0.032, respectively).

Conclusion: Our results show that UTI is still a significant problem in patients with myelodysplasia. In addition, they show that use of prophylactic antibiotic may increase the frequency of development of resistance and co-trimoxazole used for this objective is not a good option..
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Key words: Antibiotic resistance, myelodysplasia, clean intermittent catheterization, urinary tract infection

Introduction

The main objective in the follow-up of myelodysplasic patients is prevention of renal parenchymal damage due to dysfunction of lower urinary tract. Disorders in the lower urinary tract including hyperreflexic bladder, decreased adaptation and detrusor-sphynther dysynergia cause to a bladder which functions with a high pressure and incomplete emptying of the bladder. This causes to secondary vesicouretheral reflux and hydronephrosis and ultimately renal parencymal damage develops with the contribution of urinary tract infections (UTI) (1-4).

Clean intermittent catheterization (CIC) to protect renal parencyma by decreasing upper urinary tract disorders is used as a safe and efficient method in these patients and decreases progression to chronic renal disease (4). However, administration of CIC itself increases the frequency of significant bacteriuria in patients with myelodysplasia (5, 6). Although prophylactic antibiotic is commonly used to decrease the risk of bacteriuria and UTI with fevet in patients in whom clean intermittent catheterization is administered, studies have shown that

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use of prophylactic antibiotic does not eliminate bacteriuria, but causes to an increase in the frequency of symptomatic UTI arising from resistant microorganisms (7, 8).

Thus, currently, bacteriuria and UTI are observed frequently in children with myelodysplasia despite many treatment and prophylactic treatment options. In addition, it is observed that there is no consensus between centers in terms of diagnosis of bacteriuria and symptomatic UTI as well as treatment and prevention (9, 10). In this study, it was aimed to evaluate the frequency of significant bacteriuria and antibiotic resistance patterns in children with myelodysplasia in whom CIC was administered and to determine the risk factors in terms of development of UTI and renal damage.

Material and Methods

Seventy-one patients who were found to have significant bacteriuria among 126 patients with myelodysplasia who were being followed up in Medeniyet University, Göztepe Education and Research Hospital, Pediatric Nephrology Unit between August 2011 and august 2012 were included in this study. The patients who underwent bladder augmentation operation, who had no need for regular CIC and who had infection foci other than UTI were not included in the study. The control group consisted of 49 patients who were being followed up in our clinic with a diagnosis of urinary tract infection who had no known previous genitourinary system disease. Approval was obtained from the local ethics committee for the study (14/02/2012-19/E).

While urine samples were obtained by uretheral catheterization in the patient group, they were obtained by mid-stream urine, urine bag and/or uretheral catheteriation methods in the control group. Blood samples were obtained from the patients simultaneously for complete blood count, highly specific C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) measurements.

A growth above 10^4 CFU/mL in blood samples obtained by uretheral catheter and a growth above 10^5 CFU/mL in blood samples obtained by mid-stream urine collection method or urine bag method was considered significant bacteriuria. The urine samples were planted in Mc Conkey/blood agar medium at 37°C with a specific method for culture and it was checked if growth occured 24 hours later. Antibiotic sensitivity was investigated by disc diffusion method in urine cultures.

Among the patients with myelodysplasia who were found to have significant bacteriuria, the ones who had a change in the pattern of fever, side/abdominal pain and mixion and/or urinary colur and odor and the ones who had systemic inflammatory response (increase white blood cell count, CRP and or ESR) as long as there was no other focus to explain the present infection state were defined to have symptomatic UTI (11). The patients who did not have these criteria were defined to have asymptomatic bacteriuria.

Results

The demographic properties, microorganism types found in urine culture and antibiotic resistances in the patient and control groups are shown in Table 1. No significant difference was found between the patient and control groups in terms of age and gender ($p>0.05$ and $p>0.05$, respectively).

E. coli was found in 66,2% of the patient group and 83,7% of the control group as the most common microorganism (Table 1). No significant difference was found when the patient and control groups were classified as *E. coli* and non-*E. coli* microorganisms in terms of microorganism types grown ($p=0.055$). When the antibiogram resistance properties were compared between the two groups, the rate of resistance to cotrimoxazole was found to be significantly higher in the patient group compared to the control group ($p=0.001$) (Table 1). When the patients in whom only *E. coli* was grown, the rate of cotrimoxazole resistance was found to be significantly higher in the patient group ($p=0.006$).

84.5% of the patient group was receiving prophylactic antibiotic treatment regularly. The most commonly used antibiotic for prophylaxis was cotrimoxazole and this was followed by nitrofurantoin (Table 2). In the patient group, the frequency of microorganism types which grew in urine culture did not show a significant difference between the subjects who received and did not receive prophylactic antibiotic, the frequency of cotrimoxazole resistance was found to be significantly higher in the subjects who received prophylactic antibiotic ($p=0.025$) (Table 2). No significant difference was found between the subjects who received and did not receive prophylactic antibiotic in terms of other antibiotic resistance rates (for each $p>0.05$) (Table 2).

Symptomatic UTI was found in 15 subjects (21%) in the patients group and asymptomatic bacteriuria was found in the remaining 56 subjects (79%). The diagnosis of symptomatic UTI was made in the outpatient follow-up in 9 patients and at presentation to emergency department because of complaints including mainly fever in 6 patients. When these two patient groups were compared, the frequencies of abdominal/side pain and nausea/vomiting and the mean white blood cell count, hs-CRP level and ESR were found to be significantly higher in symptomatic patients (Table 3). When the microorganism types grown in urine culture were classified as *E. coli* and non-*E. coli* microorganisms, no significant difference was found between the two patient groups (Table 3).

Discussion

The results of this cross-sectional study show that significant bacteriuria develops in approximately 56% of children with myelopdysplasia despite current medical therapies and symptomatic UTI develops in approximately 1/5. In the literature, it has been reported that significant bacteriuria is observed in 60-70% of myelodysplasic children (5). Clean intermittent catheterization increases the frequency of significant bacteriuria, but it decreases the frequency of symptomatic UTI, since it prevents development of hydronephrosis and vesicouretheral reflux (5, 12). This rate was reported to be 5-20% in previous studies. In our study, E.coli was found as the most common cause of significant bacteriuria (12, 13). When the control group was compared with the patients with myelodysplasia in terms of microorganism types, an increase was observed in the rates of growth of non-E.coli

Table 1. Demographic properties, microorganism types found in urine culture and antibiotic resistance properties in the myelodysplasic patients and control group

	Patient group n (%)	Control group n (%)	p
Demographic Properties			
Patient number	71	49	
Age. years (mean±sd)	8.20±4.57	7.94±4.17	0.652*
Gender Female/Male	39/32	29/20	0.710
Microorganism types found in UC			
E. coli	47 (66.2)	41 (83.7)	0.055
Non-E. coli microorganisms			
Klebsiella spp.	10 (14.1)	5 (10.3)	
Enteroccus spp.	6 (8.5)	1 (2)	
Pseudomonas spp.	4 (5.6)	-	
Proteus spp.	2 (2.8)	1 (2)	
Enterobacter spp.	1 (1.4)	1 (2)	
Citrobacter spp.	1 (1.4)	-	
Antibiotic resistance properties			
Ampicillin	52 (80)	35 (72.9)	0.510
Co-trimoxasole	46 (76.7)	20 (41.7)	0.001
Cefazolin	24 (39.3)	17 (35.4)	0.325
Cefotaxim	16 (25.8)	14 (29.2)	0.575
Nitrofurantoin	12 (19)	5 (10.4)	0.552
Seftazidime	8 (12.7)	8 (12.5)	0.825
Levofloksasin	7 (10.1)	2 (4.3)	0.860
Netilmycin	6 (9.4)	7 (14.9)	0.388
Cefaperazon-Sulbactam	4 (6.6)	1 (2.2)	-
Amikacin	1 (1.6)	2 (4.2)	-
Imipenem	1 (1.6)	-	-

UC: urine culture; *Mann-Whitney U test; the rates of the two groups were compared using Chi-square test

microorganisms which approached to the limit of significance (11). When the resistance properties of antibiotics were examined between myelodysplasic patients and the control group, no significant difference could be found except for cotrimoxazole. Cotrimoxazole resitance was found with a higher rate in myelodysplasic patients compared to the control group.

Prophylactic antibiotic is commonly used in children with myelodysplasia and the most commonly preferred antibiotics include cotrimoxazole and nitrofurantoine (5, 9, 10). However, it has been shown that prophylactic antibiotic use does not eliminate bacteriuria and in contrast increases the frequency of symptomatic UTI due to resistant microorganisms (4, 7, 8). Approximately 4/5 of our patients were receiving regular prophylactic antibiotic treatment and the most commonly used antibiotic was cotrimoxazole. There was no significant difference between our myelodysplastic patients who used and did not use prophylactic antibiotic and between our myelodysplastic patients and the control group in terms of the frequencies of microorganism types found in urine cultures. The rates of cotrimoxazole resistance were found to be significantly higher in our myelopdysplasic patients compared to the control group and in our myelodysplasic patients who received prophylactic treament compared to the ones who did not receive prophylactic treatment. These results of us show that prophylactic antibiotic use may increase the frequency of development of resistance. A high rate of significant bacteriuria despite use of prophylactic antibiotic and the fact that prophylactic antibiotic leads to a significant rate of resistance raise doubts about the efficiency of prophylactic antibiotic use in the follow-up of myelodysplastic patients. Studies have shown that bacteriuria observed in patients with neurogenic bladder is frequently caused by strains with low efficiency which do not lead to symptoms and these strains do not increase renal parencymal damage (11, 14-16). In addition, these microorganisms may pro-

Table 2. Microorganism types found in urine culture of the myelodysplastic patients by the state of use of prophylactic antibiotic and antibiotic resistance properties

	Use of prophylactic antibiotic		
	Yes n (%)	No n (%)	p*
Patient number	60 (84.5)	11 (15.5)	
Prophylactic antibiotic types			
Co-trimoxazol	38 (63.3)	-	
Nitrofurantoin	10 (16.7)	-	
Cefalexin	6 (10)	-	
Cefaklor	6 (10)	-	
Microorganism types found in UC			
E. coli	39 (65)	8 (72.7)	0.318
Non-E.coli microorganisms			
Klebsiella spp.	10 (16.7)	-	
Enteroccus spp.	4 (6.6)	2 (18.2)	
Pseudomonas spp.	3 (5)	1 (9)	
Proteus spp.	2 (3.3)	-	
Enterobacter spp.	1 (1.7)	-	
Citrobacter spp.	1 (1.7)	-	
Antibiotic resistance properties			
Ampicillin	45 (80.4)	7 (77)	0.980
TMP-SMX	42 (82.4)	4 (44.4)	0.025
Cefazolin	20 (38.5)	4 (44.4)	0.187
Cefotaxim	13 (24.5)	3 (33.3)	1.000
Nitrofurantoin	12 (22.2)	-	187
Ceftazidime	6 (11.5)	2 (18.2)	0.729
Levofloxacin†	7 (12.1)	-	0.683
Netilmicin	5 (9.4)	1 (9.1)	1.000
Cefaperazon-Sulbactam†	4 (7.8)	-	
Amikacin	1 (1.9)	-	
Imipenem	1 (1,9)	-	

UC: urine culture; *Chi-square test; †Fisher's Exact test

vide a biological protective treatment by preventing growth of pathogenic strains. Thus, screening of asymptomatic bacteriuria is not recommended in these patients (13, 15). Prophylactic antibiotic treatment should be limited to the patients below the age of one who have the highest risk for renal parencymal damage and the patients who have a high risk in terms of upper urinary tract damage and antibiotic selection should be done considering regional resistance properties.

There is still no consensus between centers in terms of the diagnosis and treatment of symptomatic UTI (9, 10). Absence of ordinary findings because of frequent pyuria and_neurological sensory loss may lead to difficulties in the diagnosis of asymptomatic bacteriuria and symptomatic UTI (13). In such cases, presence of systemic inflammatory response may be directive (17). In our study, hs-CRP and ESR were measured for the diagnosis of symptomatic UTI and side pain and vomiting as well as fever were significant findings which supported symptomatic UTI. Some centers treat 50 leucocytes or more in one high power field in presence of asymptomatic significant bacteriuria (9). In our study, more leukocyturia was observed in patients with symptomatic UTI, but the sensitivity and specificity of pyuria alone in the absence of fever and other symptoms is open to discussion in these patients. A direct relation has been shown between recurrent UTI with fever and renal damage in myelodysplasic patients and it has been recommended that urodynamic

Table 3. Clinical and laboratory properties in myelodysplastic patients according to presence of symptomatic or asymptomatic bacteriuria

	Symptomatic UTI (n=15)	Asymptomatic bacteriuria (n=56)	p
Demographic properties			
Gender. Female/Male	9/6	30/56	0.879†
Age. years	8.56±4.69	8.11±4.25	0.730*
Clinical signs and symptoms			
Abdominal/side pain	5 (333)	5 (8.9)	0.029†
Nausea/vomiting	4 (26.7)	3 (5.4)	0.032†
Constipation	9 (60)	26 (46.4)	0.350†
Urine discoloration	9 (60)	28 (50)	0.691†
Change of odor of urine	9 (60)	29 (51.8)	0.783†
Laboratory properties			
Serum			
WBC	11.9±3.7	8.85±2.7	0.003*
CRP	7.43±6.7	0.6±1.3	0.001*
ESR	62.9±24.7	26±18.8	0.001*
Complete Urinalysis			
WBC	140±129.8	77.8±99.8	0.011*
Erythrocyte number	6.1±7.1	8.7±20.2	0.607*
Leukocyte esterase positivity	15 (100)	52 (92.9)	0.287†
Nitrit positivitiy	10 (66.7)	45 (80.4)	0.260†
Presence of bacteria	7 (46.7)	35 (62.5)	0.417†
Microorganism types found in UC			0.199†
E. coli	12 (80)	35 (62.5)	
Non-E. coli microorganisms	3 (20)	21 (37.5)	

†Chi-square test; *Mann-Whitney U test

Catergorical variables were expressed as n (%), continuous variables were expressed as mean±sd.

UTI: urinary tract infection; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate

findings should be evaluated in myelodysplasic patients even if vesicouretheral reflux is absent (14, 18).

The results of this study show that UTI is still an important problem in children with myelodysplasia in whom CIC is performed. On the other hand, the efficiency of prophylactic antibiotic treatment in the follow-up of myelodysplasic patients is open to discussion because of observation of a high rate of significant bacteriuria and development of resistance with a significant rate. In addition, this study shows that cotrimoxazole is not a good option in patients who carry a high risk for upper urinary tract disorder in which prophylactic antibiotic treatment is considered.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University (14.02.2012-19/E).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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