

Clinical Risk Factors for Extended Spectrum B-lactamase-producing Bacteriuria in Children with Myelodysplasia Performing Clean Intermittent Catheterization

Temiz Aralıklı Kateterizasyon Yapan Miyelodisplazili Çocuklarda Geniş Spektrumlu B-laktamaz Üreten Bakteriüri için Klinik Risk Faktörleri

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What's known on the subject? and What does the study add?

Resistant urinary tract infections make treatment difficult in patients with myelodysplasia using clean intermittent catheterization. This study will determine the clinical risk factors for bacterial resistance formation and may be effective in preventing bacterial resistance development.

Abstract

Objective: To evaluate the clinical risk factors contributing to the development of extended spectrum beta-lactamase (ESBL)- producing asymptomatic bacteriuria in myelodysplastic children performing clean intermittent catheterization (CIC).

Materials and Methods: The clinical risk factors for ESBL-producing bacteriuria were retrospectively investigated in 60 myelodysplastic children who had asymptomatic bacteriuria and were performing CIC. A total of 60 children were included in this study, 30 children (17 females, 13 males) with ESBL-positive bacteriuria in urine culture were identified as the study group and 30 age- and gender-matched ESBL-negative children (16 females, 14 males) served as controls. All children had neurogenic bladder due to myelodysplasia and had been used anticholinergics. The two groups were compared in terms of age, gender, presence of constipation and motor deficit, antibiotic prophylaxis, number of hospital admission, ultrasound findings, and presence of renal scarring in dimercapto succinic acid scintigraphy and urodynamic findings.

Results: The mean age of the children was 77±50 months in study and 78±69 months in control groups. There was no statistically significant difference in terms of maximum bladder capacity, leak point pressure, constipation status and scarring. In study and control groups, 83% and 46% of children were on antimicrobial prophylaxis, respectively (p=0.007).

Conclusion: ESBL-producing bacteriuria was found to be associated with long-term antibiotic prophylaxis. Thus, it was concluded that the use of antibiotics for asymptomatic bacteriuria should be kept to a minimum.

Keywords: Antibiotic prophylaxis, ESBL producing bacteriuria, Myelodysplasia

Öz

Amaç: Bu çalışmada, temiz aralıklı kateterizasyon yapan miyelodisplastik çocuklarda genişlemiş spektrumlu beta-laktamaz (ESBL) üreten asemptomatik bakteriüri gelişimine yol açan klinik risk faktörleri araştırıldı.

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Gereç ve Yöntem: Asemptomatik bakteriürisi bulunan ve temiz aralıklı kateterizasyon yapan 60 miyelodisplastik çocuk ESBL üreten bakteriüri için klinik risk faktörleri açısından geriye dönük olarak incelendi. Bunların 30'unda (17 kız, 13 erkek) idrar kültüründe ESBL pozitif bakteriüri saptandı ve çalışma grubu olarak belirlendi. Yaş ve cinsiyet açısından çalışma grubuna benzer şekilde, kontrol grubu olarak ESBL-negatif üremesi olan 30 (16 kadın, 14 erkek) çocuk çalışmaya dahil edildi. Tüm çocuklarda miyelodisplazi nedeniyle nörojenik mesaneye sahipti ve antikolinerjik kullanmaktaydılar. Gruplar yaş, cinsiyet, kabızlık, antibiyotik profilaksisi, hastaneye başvuru sayısı, ultrason bulguları, dimercapto süksinik asit renal skar ve ürodinamik bulgular açısından karşılaştırıldı.

Bulgular: Çocukların yaş ortalaması çalışma grubunda 77 ± 50 ay, kontrol grubunda 78 ± 69 aydı. Tablo 1 ve 2 bu çalışmada değerlendirilen tüm parametreleri göstermektedir. Antimikrobiyal profilaksi açısından gruplar arasında istatistiksel olarak anlamlı fark vardı. Çalışma grubunda çocukların %85'i, kontrol grubunda %46'sı antimikrobiyal profilaksi almaktaydı.

Sonuç: Antibiyotik profilaksisi ESBL üreten bakteriüri insidansını artırmaktadır. Bu nedenle, özellikle asemptomatik bakteriüri için antibiyotik kullanımı kısıtlanmalıdır.

Anahtar Kelimeler: Antibiyotik profilaksisi, ESBL-üreten bakteriüri, Miyelodisplazi

Introduction

Children with myelodysplasia most probably will develop neurogenic bladder dysfunction, and after that pyuria or bacteriuria. Clean intermittent catheterization (CIC) and antimuscarinic treatment is probably required to prevent future renal damage for these children group (1). CIC is crucial for children who void ineffectively. An increase in intravesical pressure leads to the risk of upper urinary tract deterioration and also urinary tract infections (UTIs) and vesicoureteral reflux (VUR) (1). The majority of myelodysplastic children who perform CIC present with asymptomatic bacteriuria. Although antibiotic treatment is not required for asymptomatic bacteriuria, it is still necessary prior to some urological procedures such as urodynamic study and voiding cystourethrography. Generally, gram-negative bacilli are the most common causes of UTIs (2). Although these pathogens are resistant to many antibiotics in the hospital setting, most of the causes of community-acquired UTIs are susceptible to antibiotics. However, it has been shown that antimicrobial-resistant pathogens, including *Escherichia coli* (*E. coli*), which produce extended-spectrum β -lactamase (ESBL), can cause community-acquired UTIs (3). ESBL-producing bacteriuria makes treatment difficult due to antibiotic resistance. Need for parenteral treatment may necessitate hospitalization in these situations. Although optimal antimicrobial therapy has been carefully considered, the frequency of isolated pathogens and the clinical history of patients who developed ESBL-producing bacteriuria remain largely unclear. Therefore, the current study retrospectively analyzed bacteriological characteristics and clinical features of patients with and without ESBL-producing bacteriuria.

Materials and Methods

This study was performed in the Marmara University Faculty of Medicine between March 2015 and March 2019 and in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was not received due to the

retrospective nature of the study. Written informed consent was obtained from the patients or his/her relatives. Medical records of 120 children diagnosed with myelodysplasia and asymptomatic bacteriuria and performing CICs were retrospectively reviewed. According to the definition of the European Urology Association (4), patients with fever, malaise, suprapubic pain and dysuria were accepted as having symptomatic UTI. Uropathogens that did not cause a symptomatic response in the host but grew in urine culture were accepted as asymptomatic bacteriuria. Asymptomatic UTI may include leukocyturia but no other symptoms. Among these children, 30 children (13 males, 17 females) with ESBL-producing bacteriuria in urine culture were identified as the study group and among the remaining 90 children, 30 age- and gender-matched children (14 males, 16 females) with ESBL-negative bacteriuria were taken as the control group. ESBL-producing bacteriuria was diagnosed based on the results of the double disc synergy test (5). All children had neurogenic bladder due to myelodysplasia and were performing CICs and using anticholinergics. The groups were compared in terms of age, gender, presence of constipation and motor deficit, antibiotic prophylaxis, number of hospital admissions, ultrasound, urodynamic and voiding cystourethrography findings and presence of renal scarring in Dimercapto Succinic Acid scintigraphy (DMSA). DMSA scintigraphy was performed to assess permanent renal scarring at least 6 months after the last febrile UTI. Retrospectively, amoxicillin (50 mg/kg), nitrofurantoin (1 mg/kg) and sulfamethoxazole-trimethoprim (50-10 mg/kg) were used for continuous prophylaxis in both groups.

Statistical Analysis

The IBM SPSS Statistics 22 (SPSS IBM, Türkiye) program was used for statistical analysis in the evaluation of the findings obtained in this study. While evaluating the data of the study, the suitability of the parameters to normal distribution was evaluated by means of the Kolmogorov-Smirnov test and Shapiro-Wilks test and it was found that the parameters did not show normal distribution. The quantitative data and descriptive

statistical values, such as frequency, mean and standard deviation were compared with the Mann-Whitney U test. For qualitative data, the Fisher-Freeman-Halton test was used. A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the children in the study and control groups was 77 months (5-216) and 78 months (minimum: 2-240), respectively. The male-to-female ratio was 13:17 in the study and 14:16 in the control group. Lesions were located in lumbar (n=24, n=26), lumbosacral (n=4, n=3) and sacral (n=2, n=1) regions of the spinal cord, in study and control group, respectively. Table 1 and 2 demonstrate the comparison of all parameters assessed in this study between the two groups.

There was a significant difference in the number of patients receiving antibiotic prophylaxis between the groups. 83% of the patients in the study group and 46% in the control group were on antimicrobial prophylaxis. Among the patients using antimicrobial prophylaxis in the study group, 15 children (60%) received sulfamethoxazole-trimethoprim (50-10 mg/kg), 7 (28%) received amoxicillin (50 mg/kg) and 3 children (12%) received nitrofurantoin (1 mg/kg) prophylaxis, and in the control group, 8 children (57%) received sulfamethoxazole-trimethoprim (50-10 mg/kg), 4 (28%) received amoxicillin (50 mg/kg) and 2 children (14%) received nitrofurantoin (1 mg/kg) prophylaxis. Although the number of hospital admissions was higher in children in the study group, the difference was not found to be statistically significant. As shown in Table 3, there were 10 children in the study group, and 6 children in the control group with radiologically proven VUR. 3 of the 10 children in the study group and 1 of the 6 children in the control group had bilateral VUR. In the study group, bladder dynamics were worse compared to those in the control group but there was no statistically significant difference. Upper urinary tract deterioration rates were similar in

	ESBL (+)	ESBL (-)	p
	Mean ± SD (median)	Mean ± SD (median)	
Age (month)	77.47±50.01 (66.5)	78.33±69.99 (48)	0.599
Mean number of hospital attendance in 2 years	8.3±5.82 (7)	5.57±3.2 (5)	0.069
Max bladder capacity (mL)	148.5±85.97 (140)	174.13±128.11 (149.5)	0.663
LPP (cm H ₂ O)	51.73±43.02 (34)	46±44.61 (30.5)	0.311
Mann-Whitney U test ESBL: Extended spectrum beta lactamase, LPP: Leak point pressure, SD: Standard deviation			

both groups. *E. coli* accounted for most of the bacteria detected in both groups, as shown in Table 4. Before the detection of ESBL-producing bacteriuria, common bacteria included *E. coli*, *Enterococcus faecalis* and *Klebsiella pneumoniae*. In total, 34 and 36 strains were isolated from the urine in the study and control groups, respectively. In the study group, 3 children had multiple pathogens identified simultaneously in the urine culture (one child had 3 pathogens and the other two had two pathogens in their urine culture). In the control group, 4 children had multiple pathogens at the same time in urine culture (two children had 3 pathogens and the others had two pathogens in their urine culture). One patient in each group with multiple growths in urine culture had *Staphylococcus epidermidis* growth in urine culture. It was considered contamination. One patient in control group with multiple growths in urine culture had *Morganella*

merge		ESBL (+)	ESBL (-)	p
merge		n (%)	n (%)	merge
Gender	Boy	13 (43.3%)	14 (46.7%)	11.000
	Girl	17 (56.7%)	16 (53.3%)	-
Constipation	Yes	16 (53.3%)	16 (53.3%)	11.000
	No	14 (46.7%)	14 (46.7%)	-
Antimicrobial prophylaxis	Yes	25 (83.3%)	14 (46.7%)	10.007*
	No	5 (16.7%)	16 (53.3%)	-
Scar in DMSA	No	23 (76.7%)	25 (83.3%)	20.885
	One sided	5 (16.7%)	3 (10%)	-
merge	Two sided	2 (6.7%)	2 (6.7%)	-
1: Continuity (yates) correction, 2: Fisher-Freeman-Halton test, *: p<0.05, ESBL: Extended spectrum beta lactamase, DMSA: Dimercapto Succinic Acid scintigraphy				

Grade of VUR (right and left)	Study group	Control group	p
1 and 0	1	2	-
0 and 1	2	0	-
1 and 1	1	0	-
0 and 2	1	0	-
2 and 0	2	1	-
0 and 3	0	1	-
3 and 0	0	1	-
3 and 2	0	1	-
4 and 0	1	0	-
2 and 4	1	0	-
3 and 4	1	0	-
Total	10	6	0.15
Mann-Whitney U test, VUR: Vesico ureteral reflux			

morganii growth. It was also considered contamination. Table 4 shows the number of strains isolated from urine in the study and control groups.

Table 4. Numbers of strains isolated from urine in study and control groups

Study group	No. of strains (%)	Control group	No. of strains (%)
<i>Escherichiacoli</i> [ESBL (+)]	23 (76.6)	<i>Escherichia coli</i>	15 (50)
<i>Klebsiella pneumonia</i> [ESBL (+)]	3 (10)	<i>Klebsiella pneumoniae</i>	5 (16.6)
Proteus [ESBL (+)]	1 (3.3)	<i>Enterococcus faecalis</i>	2 (6.6)
<i>Escherichiacoli</i> [ESBL (+)] <i>Klebsiella pneumonia</i>	1 (3.3)	<i>Proteus mirabilis</i>	2 (6.6)
<i>Staphylococcus epidermidis</i>	-	<i>Staphylococcus epidermidis</i>	1 (3.3)
<i>Escherichiacoli</i> [ESBL (+)] Enterococcus faecalis	1 (3.3)	<i>Staphylococcus hominis</i>	1 (3.3)
	1 (3.3)	<i>Escherichia coli</i> <i>Klebsiella pneumonia</i> <i>Enterococcus faecalis</i>	1 (3.3)
<i>Klebsiella pneumonia</i> [ESBL (+)] <i>Proteus mirabilis</i>		<i>Escherichia coli</i> <i>Klebsiella pneumonia</i> <i>Staphylococcus epidermidis</i>	1 (3.3)
		<i>Klebsiella pneumoniae</i> <i>Morganella morganii</i>	1 (3.3)
		<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i>	1 (3.3)
Total	30 (100%)		30 (100%)

ESBL: Extended spectrum beta lactamase

Discussion

Children who perform CIC often have bacteriuria. For patients performing CIC, 102 or more colony forming units per mL is the standard definition for bacteriuria (6). Asymptomatic bacteriuria is a significant and frequent clinical problem in patients with myelodysplasia, especially in those with neurogenic bladder. Although no treatment is required, urine should be sterilized prior to some procedures such as urodynamic examination and voiding cystourethrography. The most common causes of asymptomatic bacteriuria are gram-negative bacilli, specifically *E. coli* (7). In our study, *E. coli* accounted for 83% and 60% of the isolated pathogens in study and control groups, respectively. The progressive increase in the incidence of ESBL-

producing bacteriuria is an important problem for patients with community-acquired UTIs, especially in children performing CICs. For proper CIC, in addition to sterile implementation techniques, an appropriate interval and adequate fluid intake are important. It is also important that recommendations on the appropriate technique for CIC implementation are given to children and their caregivers. A study performed in Japan has shown that the most important factors for future renal prevention were sufficiently frequent catheterization and prevention of bladder overfilling (8). In a study conducted in Turkiye, long-term prophylaxis, being below one year of age, and performing CIC were shown to be risk factors for ESBL production (9). In another study, hospitalization within the previous month, antibiotic use in the past 3 months, and neurological diseases were reported to be risk factors for UTI due to ESBL-producing *E. coli* (3). In another study conducted in Turkiye, hospitalization, presence of an underlying disease, and antibiotic use within the previous 3 months were shown to be potential risk factors (10). A survey in France analyzing 1,000 hospitalizations showed that the number of ESBL-producing bacteria isolates increased four-fold in 10 years (11). Antimicrobial prophylaxis for VUR decrease the risk of febrile or symptomatic UTIs in children receiving prophylaxis by 50% compared to children receiving placebo (12). However, the effect of prophylaxis is controversial. Clarke et al. (13) have reported that use of prophylactic antibiotics increased the incidence of UTI due to the development of resistant pathogens. The reasons for ESBL-producing bacteriuria may be multifactorial, but it is noteworthy that low-dose, long-term antibacterial prophylaxis, presence of an underlying disease and hospital admissions and hospitalization are important risk factors. In this study, the rate of antimicrobial prophylaxis in the study group with ESBL-producing asymptomatic bacteriuria was significantly higher than in the control group. Although the number of hospital admissions was higher in study group, this was not statistically significant. This may be a result of low number of patients included in our study.

Study Limitations

Its retrospective nature and small sample size were the limitations. In addition, the patients were not evaluated for the history of any surgical intervention that may play a role in ESBL production.

Conclusion

The use of antibiotics for asymptomatic bacteriuria should be kept to a minimum and further prospective studies are needed for more definitive conclusions.

Ethics

Ethics Committee Approval: This study was performed in the Marmara University Faculty of Medicine between March 2015

and March 2019 and in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was not received due to the retrospective nature of the study.

Informed Consent: Written informed consent was obtained from the patients or his/her relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.A., T.T., Design: T.T., C.A., Data Collection or Processing: T.T., Y.T., Analysis or Interpretation: Ç.A.Ş., Y.T., A.Ş., Literature Search: A.G., M.S., Writing: T.T.

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