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Geç Sevk Edilen Miyelomeningoselli Çocuklarda İdrar Yolu Enfeksiyonu, Böbrek Hasarı ve Ürodinamik Bulgular

Urinary Tract Infection, Renal Damage and Urodynamic Findings in Late Referral Children with Myelomeningocele

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ÖZ

Giriş: Miyelomeningoselli çocuklar, nörojen mesaneye bağlı olarak tekrarlayan idrar yolu enfeksiyonu (İYE) ve böbrek hasarı açısından yüksek risk altındadır. Bu çalışmada, geç sevk edilen miyelomeningoselli çocuklarda tekrarlayan idrar yolu enfeksiyonu, böbrek hasarı ve ürodinamik bulgular arasındaki ilişkinin değerlendirilmesi amaçlandı.

Yöntem: Miyelomeningoselli hastaların dosya verileri retrospektif olarak değerlendirildi. Tekrarlayan İYE iki veya daha fazla ateşli idrar yolu enfeksiyonu atağı olarak tanımlandı. Diferansiyel fonksiyonun <%40 olması veya renal skar ve/veya atrofi varlığı renal hasar olarak kabul edildi.

Bulgular: Yetmiş beş hastanın ortanca yaşı 7,4 yıl idi. İlk başvurudaki ortanca yaş 16 ay (6-27 ay) idi. Kırk sekiz hastada tekrarlayan İYE görüldü. Cox regresyon analizinde, vezikoüreteral reflü (VUR), rezidü idrar, azalmış mesane kapasitesi, trabeküle ve hipokompliyan mesanenin tekrarlayan İYE için risk faktörü olduğu saptandı (sırasıyla p=0,028, p=0,036, p=0,005, p=0,042). Otuz hastada böbrek hasarı tespit edildi. Böbrek hasarı ile şiddetli VUR, trabeküle mesane, hipokompliyan mesane ve temiz aralıklı kateterizasyon (TAK) arasında anlamlı ilişkiler mevcuttu (sırası ile Odds oranı: 1,724, p=0,011, Odds oranı: 1,934, p=0,038, Odds oranı: 1,452, p=0,025, Odds oranı: 3,691, p=0,014). Detrusor kaçırma noktası basıncının böbrek hasarı için belirleyici bir eşik değeri olduğu belirlendi (eşik değeri: 29,8 cm H2O, p=0,021).

Sonuç: Geç sevk edilen miyelomeningoselli çocuklarda VUR varlığı ve mesane dinamiklerindeki değişiklikler İYE tekrarlaması için önemli risk faktörleriydi. Şiddetli VUR, 29,8 cmH2O'dan yüksek detrusor kaçırma noktası basıncı, trabeküle ve hipokompliyan mesane böbrek hasarı ile ilişkiliydi.

Anahtar Kelimeler: çocukluk çağı, miyelomeningosel, tekrarlayan idrar yolu enfeksiyonu, böbrek hasarı, ürodinami

ABSTRACT

Objective: The children with myelomeningocele are at an increased risk of recurrent urinary tract infection (RUTI) and renal damage due to neurogen bladder. We aimed to evaluate of the relationship between recurrent urinary tract infection, renal damage and urodynamic findings in children with myelomeningocele who were referred late.

Method: We retrospectively evaluated the data from patients with myelomeningocele. RUTI was defined as two or more episodes of febrile urinary tract infection. The differential function <40% or the presence of renal scarring and/or atrophy were considered renal damage.

Results: The median age of 75 patients was 7.4 years. The median age at first admission was 16 months (6-27 months). RUTI was observed in 48 patients. A cox regression analysis showed that vesicoureteral reflux (VUR), increased post voiding residual urine, reduced bladder capacity, trabeculated and hypocompliant bladder were risk factor for RUTI (p=0.028, p=0.036, p=0.005, p=0.042, respectively). Renal damage was determined in 30 patients. There were significant associations between renal damage and severe VUR, trabeculated bladder, hypocompliant bladder and clean intermittent catheterization (CIC) (hazard ratio: 1.724, p=0.011, hazard ratio: 1.934, p=0.038, hazard ratio: 1.452, p=0.025, hazard ratio: 3.691, p=0.014). Detrusor leakpoint pressure (DLPP) had a predictive value for renal damage (cut-off value: 29.8 cmH2O, p=0.021).

Conclusion: The presence of VUR and the changes in bladder dynamics were important risk factors for recurrence of UTI in children with myelomeningocele who were referred late. Severe VUR, DLPP >29.8 cm H2O, trabeculated and hypocompliant bladder were associated with renal damage.

Keywords: children, myelomeningocele, recurrent urinary tract infection, renal damage, urodynamics

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INTRODUCTION

Myelomeningocele is a neural tube defect leading to an incomplete spinal canal. Children with myelomeningocele have an increased risk of recurrent urinary tract infection (RUTI) vesicoureteral reflux (VUR) due to neurogenic bladder (1). Although the upper urinary system is normal at birth, the risk of renal damage is high due to bladder dysfunction over time (2). Early recognition of patients with increased risk of kidney damage and planning of appropriate treatment are of great importance in preventing the development of kidney damage. Otherwise, treatment will be delayed due to the permanent changes in the anatomical structure of the bladder (3). Half of patients older than two years of age were found to have upper urinary tract damage (4).

In this study, we aimed to evaluate the relationship between RUTI, renal damage, and urodynamic findings in children with myelomeningocele who were referred late (after the 6th month of their life).

MATERIALS AND METHODS

The data from electronic records of the patients with myelomeningocele who were followed up in our Pediatric Nephrology Outpatient Clinic in Eskisehir Osmangazi University Faculty of Medicine between September 2010 and August 2017 were reviewed in this retrospective observational study. The data from the patients with incomplete radiological examinations, a follow-up period <2 years, and a history of urologic surgery were excluded. A detailed physical examination, biochemical analysis involving renal function, urine analysis, urine culture, and urinary ultrasound (US) were done in all patients on admission. Urine analyses were repeated every three months and when there was evidence of UTI.

A urine culture was defined as positive in the presence of a single type of organism (at least 100.000 colony-forming units/mL in the clean-catch midstream urine sample and at least 50.000 colony-forming units/mL in samples obtained by catheterization). Positive urine analysis was defined as positive nitrite leukocyte esterase or pyuria (>5 leukocyte /hpf in centrifuged specimen).

The patients were diagnosed with febrile UTI in the presence of clinical symptoms compatible with the UTI, fever ≥38 ºC, positive urine culture, and urine analysis. RUTI was defined as two or more episodes of febrile UTI. Prophylactic antibiotic treatments were used in the patients with VUR and/or RUTI.

Clean intermittent catheterization (CIC) was started four or six times in one day on patients with clinical or radiologic indicators of a hostile bladder, urodynamic disorders, renal scarring, and/or bladder emptying abnormalities. The CIC training was given to the person responsible for the care of the patients by the same trained nurse.

Hydronephrosis was defined using the Society for Fetal Urology's grading system. Trabeculation, bladder volume, and wall thickness were determined in all patients by bladder US. BWT≥ 3 mm in a filled bladder was defined as increased thickness.

A micturating cystourethrography (MCUG) was done in patients with serious illness, failure to respond to treatment with suitable antibiotics in ≤48 h, or infection with non-E.coli organism, hydronephrosis, and other findings suggest VUR, such as hydroureter, parenchymal thinning, and dilatation of calyces in the US. VUR was graded from grades 1 to 5 according to the grading system of the International Reflux Study Committee. Grade 1 and 2 VUR was defined as mild VUR, while grade 3 to 5 VUR were defined as severe VUR. Trabeculation was defined as irregularities in the contour and shape of the bladder by MCUG.

Dimercaptosuccinic acid (DMSA) scintigraphy was performed in patients with hydronephrosis, hydroureter, parenchymal thinning, and dilatation of calyces on US, RUTI, and small-sized kidneys. The DMSA scan was performed at least six months after acute FUTI in patients with recurrence of infection during follow-up. The differential function of less than 40% or the presence of renal scarring and atrophy on DMSA scintigraphy was considered renal damage. Renal cortical scarring on DMSA scintigraphy was defined as a reduced or absent radionuclide uptake, a wedge-shaped defect, or the thinning or flattening of the renal outline. The reduced differential function was defined as <45%.

Urodynamic studies were performed by the same trained nurse at the urodynamics laboratory in the Pediatric Urology Clinic. All urodynamic studies were performed using the protocol recommended by the ICCS, which uses a transurethral infusion system.

Detrusor hyperactivity was defined as involuntary detrusor contractions during the filling phase. Expected bladder capacity was defined as (age in years × 30 + 30) mL. The reduced bladder capacity was defined as < 65% of the expected bladder. Compliance was defined as the increase in detrusor pressure per unit of volume change in detrusor pressure (V/P) 5. A compliance less than 10 mL/cmH2O was defined as a hypocompliant bladder. In children ≤6 years, post-voiding residual urine volume (PVR) greater than 20 mL was defined as increased residual volume. In children ≥7 years, PVR > 10ml was considered elevated (6). The detrusor leak point pressure (DLPP) was defined as the lowest detrusor pressure causing urine leakage in the absence of increased abdominal pressure 7.

This study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki (Number: 80558721/G-226).

Statistical analyses

Statistical analyses were performed by using SPSS 11.0 (SPSS Inc, Chicago, Illinois). Values are expressed as mean and SD for continuous variables and interquartile range for qualitative variables. The Shapiro-Wilk test was used to determine normality of data. Means were compared using independent sample t-test in normally distributed data. The comparison of the nonnormally distributed data was done by using the Mann–Whitney U test. A Cox proportional hazards regression analysis was performed to determine the risk factors for RUTI and renal damage. Qualitative variables were compared using the chi-square test. A receiver operating curve (ROC) analysis was used to determine the cutoff values and the sensitivity/ specificity of the detrusor leakage pressure for prediction of renal scarring and recurrence of UTI. A p-value <0.05 was considered significant.

RESULTS

The data of 152 patients with myelomeningocele was obtained from electronic records. Twenty-four patients were missing radiological examination or follow-up time. Seven patients had a history of urologic intervention. The data from the remaining 121 patients were analysed. Forty six of these patients were followed up before the sixth month of life. The other 75 patients were followed up after the 6th month of their life. The median age at first admission to our outpatient clinic of patients who were followed up late was 16 months years (6-27 months). When the patients referred before and after six months were compared, the frequencies of RUTI and renal damage were higher in those referred after six months (Table 1).

Table 1. the Features of the Patients.

(n=75) (n=46)	Referred before 6 months	Referred after 6 months	p
Gender (Female)	41 (54.7)	20 (43.5)	0.423
Age (years)	4 (3-5)	6 (4-10)	0.043
Follow-up time (years)	3.1±0.8	3.8±1.7	0.342
Creatinine (mg/dL)	0.67±0.26	0.58±0.12	0.512
VUR	38 (50.7)	19 (41.3)	0.075
RUTI	48 (64)	16 (34.8)	0.008
Renal damage	30 (40)	11 (23.9)	0.032

Values were expressed as mean ± SD or median (interquartile range) and number (percentage).
RUTI; recurrent urinary tract infection,
VUR; vesicoureteral reflux.
A p value <0.05 was considered significant.

Fifty eight (77.3%) of late referral patients whose data were included in our study had a history of febrile UTI. RUTI was observed in 48 patients during the follow-up period. Fifty eight of the patients had a history of febrile UTI. The frequencies of VUR, increased PVR, trabeculated bladder, and reduced bladder capacity were higher in the patients with RUTI than those without RUTI (p = 0.043, p = 0.034, p = 0.002, p = 0.041), respectively (Table 2).

Renal damage was determined in 30 of the patients. The frequencies of severe VUR, trabeculated, and hypocompliant bladder were higher in the patients with renal damage than those without renal damage (p = 0.029, p = 0.031, p = 0.031, respectively, Table 3). The patients with renal damage had higher DLPP (p = 0.003). In the ROC curve analysis, DLPP had a sensitivity of 76.8% and specificity of 62.7% for the prediction of renal damage (cut-off value: 29.8 mmH2O, the area under the curve [AUC] ± SE: 0.677 ± 0.051, p = 0.021).

Table 2. The Features of The Patients with and Without RUTI.

(n=48) (n=27)	RUTI (+)	RUTI (-)	p
Gender (Female)	26 (54.2)	15 (55.5)	0.423
Age (years)	7 (3-11)	9 (7-12)	0.854
Creatinine (mg/dL)	0. 68±0.26	0.56±0.12	0.278
Hydronephrosis	13 (27.1)	6 (22.2)	0.437
VUR	27 (56.3)	11 (40.7)	0.043
Mild VUR	11 (22.9)	3 (11.1)	0.036
Severe VUR	18 (37.5)	6 (22.2)	0.039
Parenchymal thinning	9 (18.8)	3 (11.1)	0.413
Increased PVR (mL)	29 (60.4)	10 (37)	0.034
Trabeculated bladder	14 (29.2)	2 (7.4)	0.002
Bladder wall thickening	16 (33.3)	7 (25.9)	0.264
Reduced bladder capacity	31 (64.5)	12 (44.4)	0.041
Hypocompliant bladder	27 (56.3)	9 (33.3)	0.026
Detrusor leakpoint pressure	54.7±12.56	32.7±9.87	0.051
Neurogenic detrusor overactivity	20 (41.6)	8 (29.6)	0.075

Values were expressed as mean ± SD or median (interquartile range) and number (percentage).
RUTI; recurrent urinary tract infection,
VUR; vesicoureteral reflux,
PVR; post voiding residual volüme.
A p value <0.05 was considered significant.

A Cox proportional hazards regression analysis determined significant associations between RUTI and the presence of VUR, increased PVR, trabeculated and reduced bladder capacity

(hazard ratio [HR]: 1.613, p = 0.028, HR: 1.341, p = 0.036, HR: 2.131, p = 0.005; HR: 1.304, p = 0.042, respectively). There were significant associations between renal damage and severe VUR, trabeculated bladder, and hypocompliant bladder (HR: 1.724, p = 0.011, HR: 1.934, p = 0.038, HR: 1.452, p = 0.025, Table 4).

Table 3. The Features of the Patients Referred After 6 Months of Life with and Without Renal Damage.

(n=30) (n=45)	Renal damage (+)	Renal damage(-)	p
Gender (Female)	17 (56.7)	29 (64.4)	0.513
Age (years)	6 (3-12)	8 (4-11)	0.618
RUTI	26 (86.7)	22 (48.9)	0.034
Creatinine (mg/dL)	0.61±33	0.69±0.21	0.312
Hydronephrosis	11 (36.6)	8 (17.7)	0.003
VUR	21 (70)	17 (37.7)	0.037
Mild VUR	5 (16.7)	9 (20)	0.562
Severe VUR	15 (50)	9 (20)	0.029
Parenchymal thinning	7 (23.3)	5 (11.1)	0.012
Increased PVR (mL)	15 (50)	24 (53.3)	0.415
Trabeculated ladder	10 (33.3)	6 (13.3)	0.031
Bladder wall thickening	12 (40)	11 (24.4)	0.053
Reduced bladder capacity	18 (60)	25 (55.6)	0.713
Hypocompliant bladder	19 (63.3)	17 (37.7)	0.031
Detrusor leakpoint pressure	65±9.23	32±4.76	0.003
Neurogenic detrusor overactivity	10 (33.3)	18 (40)	0.352
History of RUTI	22 (73.3)	36 (80)	0.917

Values were expressed as mean ± SD or median (interquartile range) and number (percentage).

RUTI; recurrent urinary tract infection,

VUR; vesicoureteral reflux,

PVR; post voiding residual volüme.

A p value <0.05 was considered significant.

Table 4. A Cox Proportional Hazards Regression Analysis of the Association of RUTI and Renal Damage.

	RUTI		RENAL DAMAGE	
	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p
RUTI	-		1.811 (1.234-6.785)	0.001
VUR	1.613 (1.123-2.832)	0.028	1.342 (1.121-3.543)	0.023
Mild VUR	1.253 (1.108-3.102)	0.032	0.356 (0.293-1.528)	0.615
Severe VUR	1.534 (1.223-5.132)	0.016	1.724 (1.347-4.901)	0.011
Parenchymal thinning	0.563 (0.093-3.508)	0.546	1.224 (0.571-20.262)	0.179
Increased PVR (mL)	1.341 (1.203-3.243)	0.036	0.405 (0.473-4.761)	0.491
Trabeculated bladder	2.131 (1.783-32.876)	0.005	1.934 (1.283-3.876)	0.038
Bladder wall thickening	0.365 (0.293-4.089)	0.894	0.405 (0.210-2.116)	0.491
Reduced bladder Capacity	1.304 (1.123-2.345)	0.042	0.511 (0.423-2.345)	0.421
Hypocompliant bladder	1.731 (1.357-6.975)	0.038	1.452 (1.217-3.975)	0.025
Detrusor leakpoint pressure	1.023 (0.786-1.231)	0.098	4.845 (1.345-8.971)	0.004
Neurogenic detrusor overactivity	0.813 (0.526-1.497)	0.158	0.434 (0.312-0.962)	0.569
History of RUTI	-		0.712 (0.523-1.162)	0.629

RUTI; recurrent urinary tract infection,

VUR; vesicoureteral reflux,

PVR; post voiding residual volume.

A p value <0.05 was considered significant.

DISCUSSION

We investigated the risk factors for RUTI and renal damage in children with myelomeningocele who were referred late. Our results showed that the increased PVR, decreased bladder capacity, trabeculated, and hypocompliant bladder were risk factors for RUTI in children with myelomeningocele who were referred late. Severe VUR, trabeculated bladder, reduced compliance and DLPP >29.8 cmH2O were associated with renal damage.

RUTI causes significant morbidity in patients with neurogenic bladder. The increased bladder pressures, urinary stasis, and colonization of bacteria contribute to the development and recurrence of UTI. The decreased bladder emptying and residual urine can lead to increased bacterial counts in the bladder (8). Trabeculation, which is characterized by fibroproliferative changes in the bladder wall, often accompanies changes in bladder dynamics and decreased compliance (9). In one study, it was found that UTI developed in half of the patients up to the age of 15 months. This rate increased to 80% when patients reached the age of 15 years (10). In our study, febrile UTI recurred in 64% of patients during follow-up. The increased PVR, trabeculated bladder, and hypocompliant bladder were significant risk factors for recurrence of UTI. These results supported that the changes in bladder dynamics were significant risk factors for RUTI and the importance of preventing urinary stasis in reducing UTI recurrence.

VUR is related to chronic renal disease in patients with meningomyelocele. Filler et al. showed the frequency of VUR increased with age in these patients. In their study, while VUR was detected in a quarter of the patients in the first year of life, it was detected in 50% of patients up to the age of 9 (10). Although studies are showing that VUR increases the risk of RUTI, there are also studies that show the opposite (11, 12). There is also a study that found a relationship between the presence of VUR and frequent UTI but not the degree of VUR (13). In our study, VUR was detected in half of the patients. However, the presence of VUR rather than its severity was associated with the recurrence of UTI.

Children with meningomyelocele have an increased risk of renal damage because of bladder dysfunction. Up to 25 percent of patients develop renal damage over time (14). In a study involving late referred delayed children with meningomyelocele, more than half of children with renal damage had a history of RUTI (4). Contrarily, Kanaheswari et al. did not detect a significant association between renal scarring and symptomatic UTI (15). In our study, there was renal damage in 40% of the patients with meningomyelocele late referral. This high frequency of renal damage reveals the importance of starting the follow-up of patients with meningomyelocele in the early period. While febrile UTI recurrence was a significant risk factor during the follow-up, we could not find a relationship between the history of RUTI and renal damage. Since our patients were referred late, we might not have been able to determine the effect of previous febrile urinary tract infections on renal damage. Therefore, we could not clearly distinguish whether renal damage was caused by the previous febrile urinary tract infection or the one during the follow-up.

VUR is often caused by disturbances in bladder hemodynamics in meningomyelocele. The VUR, high bladder filling, and emptying pressures play an important role in the development of renal damage in patients with meningomyelocele (3). While the severity of VUR has been found to be effective in renal damage development in some studies, there are also studies showing that the severity of VUR does not affect renal damage development (16, 17). Renal damage was found to be associated with high-grade VUR in studies of children with spinal dysraphism (18). Similar to the literature, it was determined that severe VUR was a significant risk factor for renal damage in our study.

Bladder compliance is defined as the relationship between a change in detrusor pressure and a change in bladder volume. Low compliance is a significant risk factor for upper urinary tract deterioration in patients with neurogenic bladder (19). Bladder wall abnormalities accompanied by changes in collagen structure in the detrusor muscle and muscle hypertrophy lead to thickening and trabeculation in the bladder wall (20). The results of our study supported previous studies by showing that decreased compliance and trabeculation were risk factors for renal damage. Early detection of changes in bladder hemodynamics and applying necessary treatments are important in preventing damage.

DLPP is defined as the lowest value of detrusor pressure at which leakage occurs per urethra without increased abdominal pressure. The low bladder compliance, as well as increased detrusor pressure predispose to the development of renal damage by disrupting the urinary excretion from the kidney (21). It is stated that DLPP> 40 cmH2O can cause renal damage (22). In another study, nearly half of the patients with a DLPP value below 25 cmH2O had upper urinary tract damage (4). In our study, DLPP with a cut-off value of 29.8 cmH2O was risk factor for renal damage. This result suggests that patients with neurogenic bladder can have an increased risk of renal damage even if the DLPP <40 cmH2O.

Limitations of the Study

There are several limitations in our study. Firstly, this study is a retrospective study. Secondly, our study has a small number of patients.

Conclusion

The urodynamic parameters are associated with recurrence of UTI and renal damage in children with myelomeningocele who were referred late. The patients with decreased compliance and DLPP >29.8 cmH2O should be monitored more carefully in terms of renal damage. Early detection and management of the risk factors can reduce RUTI and renal damage.

Ethics Committee Approval: This study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki (Number: 80558721/G-226).

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nuran Cetin and Aslı Kavaz Tufan. The first draft of the manuscript was written by Nuran Cetin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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