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Research Article

Factors associated with abnormal dimercaptosuccinic acid (DMSA) renal scan findings in children with vesicoureteral reflux

Vezikoüreteral reflülü çocuklarda anormal dimercaptosüksinik asit (DMSA) renal tarama bulguları ile ilişkili faktörler

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ABSTRACT

Aim: This study aimed to investigate the association between abnormal dimercaptosuccinic acid (DMSA) scan results and demographic factors, vesicoureteral reflux (VUR) severity and laterality, as well as the presence of urinary tract infections (UTIs) in children diagnosed with VUR.

Material and Methods: A retrospective analysis was conducted on 39 children diagnosed with VUR. Data included age, gender, VUR grade, the presence of bilateral VUR, and UTI frequency. DMSA scans were used to assess renal scarring. Statistical comparisons were made between patients with normal and abnormal DMSA results to identify significant predictors of renal damage.

Results: The mean age of the children was 30 months, with 82% being female. VUR Grade III and above was significantly associated with abnormal DMSA findings (81.5% vs. 50%, $p = 0.046$). However, no significant difference was observed in the frequency of bilateral VUR between groups (33.3% vs. 41.7%, $p = 0.618$). Although patients with abnormal DMSA findings had a higher incidence of UTIs, this difference was not statistically significant (63.0% vs. 33.3%, $p = 0.090$).

Conclusion: While higher VUR grades were related to abnormal DMSA results, there was no significant statistical association with bilateral VUR or UTIs. These findings suggest that the severity of VUR may be a more important predictor of kidney damage.

Keywords: Vesicoureteral reflux, DMSA scan, urinary tract infections, renal scarring

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ÖZ

Amaç: Bu çalışmada, vezikoüreteral reflü (VUR) tanısı almış çocuklarda anormal dimercaptosüksinik asit (DMSA) tarama sonuçları ile demografik faktörler, VUR şiddeti ve lateralitesine ek olarak idrar yolu enfeksiyonu (İYE) varlığı arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntemler: VUR tanısı alan 39 çocuk üzerinde retrospektif bir analiz yapıldı. Veriler, yaş, cinsiyet, VUR derecesi, bilateral VUR varlığı ve İYE sıklığını içeriyordu. DMSA taramaları böbrek skarlarını değerlendirmek için kullanıldı. Anormal ve normal DMSA sonuçları olan hastalar arasında istatistiksel karşılaştırmalar yapıldı.

Bulgular: Çocukların ortalama yaşı 30 ay olup, %82'si kızlardan oluşmaktaydı. VUR derecesi III ve üzeri olan hastalarda anormal DMSA bulguları anlamlı şekilde daha yüksek bulundu (%81,5'e karşı %50, p = 0,046). Ancak, gruplar arasında bilateral VUR sıklığı açısından anlamlı bir fark bulunmadı (%33,3'e karşı %41,7, p = 0,618). Anormal DMSA bulguları olan hastalarda İYE sıklığı daha yüksek olmasına rağmen, bu fark istatistiksel olarak anlamlı değildi (%63,0'a karşı %33,3, p = 0,090).

Sonuç: Yüksek VUR dereceleri anormal DMSA sonuçları ile anlamlı bir ilişki göstermektedir. Ancak, bilateral VUR veya İYE sıklığı ile istatistiksel olarak anlamlı bir ilişki gözlenmemiştir. Bulgular, böbrek hasarının ana belirleyicisinin VUR şiddeti olabileceğini göstermektedir.

Anahtar kelimeler: vezikoüreteral reflü, dimercaptosüksinik asit taraması, idrar yolu enfeksiyonları, böbrek skarı

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) encompass a wide range of disorders, including disrupted embryonic migration of the kidneys, as well as malformations in the lower urinary system, the urine collecting system, or the development of the renal parenchyma [1]. These anomalies represent a significant cause of chronic kidney disease (CKD) and end-stage renal disease in children, accounting for nearly 30 to 50% of pediatric CKD cases [2]. The monitoring and management of these conditions in pediatric nephrology are critical to improving long-term health outcomes for affected children.

Vesicoureteral reflux (VUR) is a major cause of CAKUT, characterized by the backward flow of urine from the bladder to the ureters and kidneys [3, 4]. It can lead to recurrent urinary tract infections (UTIs) and kidney scarring, especially in high-grade cases [1, 5]. VUR severity and its complications are influenced by several factors, including the grade of reflux, presence of bladder dysfunction, and frequency of UTIs [6, 7]. Dimercaptosuccinic acid (DMSA) renal scans play a crucial role in detecting renal scarring and functional impairment, particularly in children with recurrent infections or high-grade VUR [8, 9]. Studies have shown that abnormal DMSA findings are often correlated with higher grades of VUR (grade III and above) and recurrent febrile UTIs [10]. While abnormal DMSA scans are associated with a greater risk of renal damage and long-term complications, the presence of normal scans may reduce the necessity for more invasive procedures such as voiding cystourethrography (VCUG), especially after the first UTIs [10, 11]. Despite its diagnostic value, the prevalence and determinants of abnormal DMSA findings in CAKUT patients with VUR remain under investigation [12]. Understanding these factors is essential for optimizing management strategies and preventing long-term renal damage.

This study aimed to investigate the factors associated with abnormal DMSA findings in children diagnosed with VUR, with a focus on demographic variables, VUR severity, and presence of UTIs.

Material and Methods

This retrospective study was conducted on children with VUR who were followed at the Pediatric Nephrology Clinic of the Samsun Training and Research Hospital between January 2010 and December 2017. The study adhered to the ethical regulations and principles specified in the Declaration of Helsinki and received approval from the Ethical Committee of Samsun Training and Research Hospital (Date: 17.10.2017, Decision No. 155). The requirement for obtaining informed consent was waived by the Ethics Committee due to the retrospective design of the study.

Study Population and Data Collection

A total of 520 children diagnosed with CAKUT were retrospectively evaluated to assess their eligibility for the study. Patients with other CAKUT diagnoses, such as hydronephrosis (n = 332), renal agenesis (n = 32), multicystic dysplastic kidney (n = 15), ureteropelvic junction obstruction (n = 18), ectopic kidney (n = 15), posterior urethral valve (n = 1), horseshoe kidney (n = 20), hypoplastic kidney (n = 18), duplex collecting system (n =

24), ectopic ureter (n = 1), ureterocele (n = 1), bifid pelvis (n = 2), patients lost to follow-up (n = 1), or patients with incomplete or inaccessible records (n = 1) were excluded from the study. A total of 39 patients with a VUR diagnosis were included in the analyses.

Patient data were collected using the hospital's electronic information system and patient files. These data included demographic information such as gender, and age at diagnosis, duration of follow-up; clinical parameters such as diagnoses, serum creatinine, ultrasound findings; follow-up data such as UTIs, the use of VCUG and kidney scintigraphy (99mTc-DMSA).

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of the Kolmogorov-Smirnov test are presented as mean ± standard deviation (SD) values. In contrast, non-normally distributed variables are presented as median (min-max) values. For comparisons between groups, Student's t-test and Mann-Whitney U test were used according to the normality of the distribution. Categorical variables were presented as numbers and percentages, and for inter-group comparisons, Fisher's exact test was used when the expected cell frequencies were less than 5, while the Chi-square test was used in other cases. Significance was accepted at $P < 0.05$ for all statistical analyses.

Results

The age at diagnosis ranged from 2 to 192 months, with the majority of patients being female (82.0%). All patients had abnormal prenatal and postnatal ultrasound findings. The degree of VUR was mostly Grade III (46.2%), and the frequency of bilateral VUR was 35.9%. The median follow-up time for the patients was 15 months, with a range of 3 to 84 months. UTIs were detected in 53.8% (n = 21) of the patients. UTIs were found in 16 girls (50.0%) and 5 boys (71.4%), and this difference between genders was statistically significant (p = 0.001). VCUG results were abnormal in all cases, and 69.2% had abnormal findings on the DMSA scan. The demographic and clinical characteristics of the patients are shown in Table 1.

The distribution of gender and age was comparable between patients with abnormal and normal DMSA scan results. While the ratio of VUR grade III and above was higher in the group with abnormal DMSA findings (81.5% vs. 50.0%, p = 0.046), there was no significant difference in the frequency of bilateral VUR between the groups (33.3% vs. 41.7%, p = 0.618). The frequency of UTIs appeared higher in patients with abnormal DMSA findings, but this difference did not reach statistical significance (63.0% vs. 33.3%, p = 0.090) (Table 2).

Table 1. Demographic and clinical characteristics of patients with vesicoureteral refux.

Variables	All population n = 39
Sex, n (%)	
Girl	32 (82.0)
Boys	7 (18.0)
Age at diagnosis, months	30 (2-192)
Prenatal ultrasound findings, n (%)	
Normal	-
Abnormal	39 (100)
VUR grade, n (%)	
I	2 (5.1)
II	9 (23.1)
III	18 (46.2)
IV	8 (20.5)
V	2 (5.1)
Bilateral VUR, n (%)	14 (35.9)
UTIs, n (%)	21 (53.8)
Age of diagnosis, months	7 (2-13)
Postnatal ultrasound findings, n (%)	39 (100)
Normal	-
Abnormal	39 (100)
VCUG findings, n (%)	
Normal	-
Abnormal	39 (100)
DMSA findings, n (%)	
Normal	12 (30.8)
Abnormal	27 (69.2)

DMSA, Tc-99 m dimercaptosuccinic acid; VCUG, voiding cystourethrography; VUR, vesicoureteral refux; UTIs, urinary tract infections.

Table 2. Findings associated with abnormal DMSA.

Variables	Normal DMSA n = 12	Abnormal DMSA n = 27	P-value
Sex, n (%)			
Girl	9 (75.0)	23 (85.2)	0.449*
Boys	3 (25.0)	4 (14.8)	
Age at diagnosis, months	27 (2-168)	33 (2-192)	0.135†
VUR grade, n (%)			
I-II	6 (50.0)	5 (18.5)	0.046*
>III	6 (50.0)	22 (81.5)	
Bilateral VUR, n (%)	5 (41.7)	9 (33.3)	0.618§
UTIs, n (%)	4 (33.3)	17 (63.0)	0.090*

§ Chi-square test. * Fisher's exact test. † Mann-Whitney U test. DMSA, Tc-99 m dimercaptosuccinic acid; VUR, vesicoureteral refux; UTIs, urinary tract infections.

Discussion

This study assessed the occurrence of abnormal DMSA kidney scans and the related factors in children diagnosed with VUR.

The main results showed a significant association between abnormal DMSA scans and higher VUR grades, though bilateral VUR was not significantly correlated. There was a trend toward higher UTI frequency in cases with abnormal DMSA scans.

In a study on CAKUT cases, renal scarring was detected in 13.8% of patients [13]. In children with renal ectopia, a study using DMSA scintigraphy found renal scarring in 27.9% of cases [14]. In a study of children with primary VUR, DMSA scintigraphy was normal in 14% of cases and abnormal in 86% [15]. In our study, 69.2% of patients had abnormal DMSA scan results. Additionally, gender distribution did not show a significant impact on abnormal DMSA findings. However, the majority of the study consisted of girls patients, which is consistent with some studies that report a higher incidence of VUR in girls [10, 16]. Despite this, previous research has produced conflicting results regarding the relationship between gender and VUR. Some studies suggest that VUR is more frequent in boys, particularly in the first few months of life, while others report a predominance of girl patients, especially as children grow older [17-19]. This discrepancy may be attributed to differences in the timing of diagnosis, with boys being more prone to VUR in early infancy and girls exhibiting a higher incidence later, often linked to recurrent UTIs [20]. The comparable distribution of age across both groups further reinforces that renal damage, as detected by DMSA scans, can occur at any age, influenced more by clinical factors like UTI frequency and VUR grade [16].

The study found a significant relationship between higher grades of VUR and abnormal DMSA results. Specifically, patients with VUR grade III or above were much more likely to have abnormal DMSA findings, highlighting the association between severe VUR and renal scarring [12]. In a study involving children who were diagnosed late with VUR, 83.9% of them had abnormal results on a DMSA renal scan. The median age of these children was 7.6 years, and they all had VUR of grade III to IV, which represents the more severe forms of the condition, indicating that higher grades of reflux are associated with worse kidney damage [21]. In a previous study, it was also found that abnormal DMSA rates in grade II, III, and IV were quite similar (49.4–59%), whereas grade I showed a significantly lower rate of 26.3%, and Grade 5 deviated significantly higher, with an abnormal rate of 78.8% [12]. In the RIVUR trial, the occurrence of abnormal DMSA findings varied across different VUR grades. Specifically, the rates were 7.6% for grade I, 4.7% for grade II, 10% for grade III, and significantly higher at 35.2% for grade IV [22]. These results highlight the increasing likelihood of renal scarring as the severity of VUR increases, with a notable jump from the lower to higher grades.

On the other hand, the ratio of bilateral VUR was relatively lower in patients with abnormal DMSA scan findings. A previous study demonstrated that unilateral VUR is an independent factor for abnormal DMSA scan findings, with this effect being more prominent in cases of high-grade VUR [12]. The authors proposed that this situation could be attributed to a congenitally dysplastic kidney [12]. It has been indicated that unilaterality is not related to the occurrence of renal scarring [22]. While bilateral VUR can increase the overall burden on the kidneys, it appears that the grade of reflux is a more critical factor in determining the likelihood of renal scarring. Other studies also support this conclusion, noting that renal damage is more strongly associated with the severity of VUR rather than its laterality [23, 24].

Studies have suggested a connection between DMSA scintigraphy results and recurrent UTIs [25, 26]. Studies have also indicated that febrile urinary tract infections significantly contribute to the pathophysiology of renal scarring [27-29]. In patients with abnormal DMSA scan findings, the frequency of UTIs was nearly twice as high compared to those with normal DMSA results. However, this difference did not reach statistical significance. This suggests that while UTIs are closely linked to renal scarring and abnormal DMSA results, factors such as sample size or other variables may have influenced the lack of statistical significance in this study.

This study has several limitations that should be acknowledged. First, the sample size was relatively small, which may have reduced the statistical power to detect significant differences between groups, especially in the comparison of UTI frequency between patients with abnormal and normal DMSA findings. Larger studies are needed to confirm the trends observed here. Second, the study population was drawn from a specific clinical setting, which may limit the generalizability of the findings to broader populations. Another limitation is the retrospective nature of the study. A prospective study would allow for better control over confounding variables, such as UTI frequency and management, and provide more accurate data on the timing of infections and the progression of renal damage. Lastly, the timing of the DMSA scans was not standardized across all patients. The variability in when the scans were performed following VUR diagnosis or infection

could affect the detection of renal scarring. Addressing these limitations in further research would help clarify the associations observed in this study and enhance the accuracy of its conclusions.

Conclusion

This study demonstrated a significant association between higher VUR grades and abnormal DMSA findings, indicating an increased risk of renal scarring in more severe cases. While UTIs were more frequent in patients with abnormal DMSA results, the difference was not statistically significant. The lack of a significant link between DMSA abnormalities and bilateral VUR or UTIs suggests that VUR severity is a more critical predictor of kidney damage.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Ethical Committee of Samsun Training and Research Hospital (Date: 17.10.2017, Decision No. 155).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – H.G.Ö. and Y.S., Design- H.G.Ö. and Y.S., Supervision - Y.S., Data collection and/or processing - H.G.Ö. and Y.S., Analysis and/or interpretation - H.G.Ö. and Y.S., Writing – H.G.Ö., Critical review- Y.S. All authors read and approved the final version of the manuscript.

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