Evaluation of Serum Renalase in Children with Recurrent Urinary Tract Infection and Renal Scars

Tekrarlayan İdrar Yolu Enfeksiyonu ve Renal Skarı Olan Çocuklarda Serum Renalazın Değerlendirilmesi

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ABSTRACT

Objective: Recurrent urinary tract infections (UTI) are important risk factors for renal scarring. The aim of the study was to assess the relationship between renalase and renal scars in children.

Material and Methods: The study included 78 patients with recurrent UTI and 20 healthy controls. All patients had voiding cystourethrography and dimercaptosuccinic acid (DMSA) scintigraphy. Serum renalase level were analyzed in children with recurrent UTI and controls.

Results: The study included the 78 patients with a history of recurrent UTI (7 boys, 9.0%; 71 girls, 91.0%) and 20 healthy children (3 boys, 15%; 17 girls, 85%) were included in the study. The mean age of the patients and healthy controls were 11.71±0.91 years and 12.35±1.83 years, respectively. Vesicoureteral reflux (VUR) was detected in 48.7% of patients (38/78). Of 45 recurrent UTI with renal scar, 71% also had VUR. The renalase level of the recurrent UTI group was found to be significantly higher than the control group (p=0.014). Renalase level was found to have a significant relationship with renal scars. The mean renalase level of the scar group was found to be significantly higher than the scar-free group (p=0.005). It was found that there was no statistical difference between the renalase means of children with scars depending on whether they had VUR or not (p=0.688).

Conclusion: This study suggests that renalase may play an important role in the formation of renal fibrosis and scars. After clarifying the role of renalase in renal scarring, it might come up as a new agent to prevent fibrosis and scar tissue development in patients with recurrent urinary tract infections.

Key Words: Children, Recurrent UTI, Renalase, Renal scar, Vesicoureteral reflux

ÖZ

Amaç: Tekrarlayan idrar yolu enfeksiyonları (İYE), böbrek skarlaşması için önemli bir risk faktörüdür. Çalışmanın amacı çocuklarda renalaz düzeyleri ile böbrek skarları arasındaki ilişkiyi değerlendirmekti.

Gereç ve Yöntemler: Çalışmaya tekrarlayan İYE geçiren 78 hasta ve 20 sağlıklı kontrol dahil edildi. Tüm hastalara işeme sistoüretrografisi ve dimerkaptosüksinik asit (DMSA) sintigrafisi çekildi. Tekrarlayan İYE geçiren çocuklarda ve kontrollerde serum renalaz düzeyi analiz edildi.

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Bulgular: Çalışmaya tekrarlayan İYE öyküsü olan 78 hasta (7 erkek, %9.0; 71 kız, %91.0) ve 20 sağlıklı çocuk (3 erkek, %15; 17 kız, %85) dahil edildi. Hastaların ve sağlıklı kontrollerin yaş ortalaması sırasıyla 11.71±0.91 yıl ve 12.35±1.83 yıldı. Hastaların %48.7'sinde (38/8) Vezikoüreteral reflü (VUR) tespit edildi. Tekrarlayan İYE' lerin 45'inde skar, bunların da %71'inde VUR vardı. Tekrarlayan İYE grubunun renalaz düzeyi kontrol grubuna göre anlamlı olarak yüksek bulundu (p=0.014). Renalaz düzeyinin böbrek skarları ile anlamlı bir ilişkisi olduğu bulundu. Skarlı grubun ortalama renalaz düzeyi skarsız gruba göre anlamlı olarak yüksek bulundu (p=0.005). Skarlı çocukların renalaz ortalamaları arasında VUR olup olmamasına göre istatistiksel olarak farklılık olmadığı belirlendi (p=0.688).

Sonuç: Bu çalışma renalazın renal fibrozis ve skar oluşumunda önemli bir rol oynayabileceğini düşündürmektedir. Renalazın renal skarlaşmadaki rolünün aydınlatılmasının ardından tekrarlayan idrar yolu enfeksiyonu olan hastalarda fibrozis ve skar dokusu gelişiminin önlenmesinde yeni bir ajan olarak gündeme gelebilir.

Anahtar Sözcükler: Çocuklar, Tekrarlayan idrar yolu enfeksiyonu, Renalaz, Renal skar, Vezikoüreteral reflü

INTRODUCTION

Urinary tract infections (UTI) are one of the most common infections in childhood, and approximately one-third of children experience recurrent infections after an initial UTI, especially during the first six to 12 months. In UTI, acute clinical findings such as irritability, vomiting, decreased sucking, fever, dysuria, urinary frequency and flank pain may be observed, and permanent kidney scarring may also develop (1,2). The rate of renal scarring increases significantly, especially after the third UTI (3).

The most common cause of chronic kidney disease in American, Italian, Belgian and Turkish children is congenital structural anomalies of the kidneys and urinary tract (4,5). Vesicoureteral reflux (VUR), a risk factor for recurrent UTI and renal scarring, is detected in approximately 40% of patients investigated for first UTI (1,6). Early diagnosis and follow-up of VUR and renal scars are important and Tc-DMSA scintigraphy is the gold standard in detecting renal scars (7). There is a need to investigate new, more useful and noninvasive markers detect scars.

Renalase is a monoamine oxidase primarily originating from the renal proximal tubule, responsible for the degradation and inactivation of catecholamines. Renalase also exhibits cytoprotective (including cardioprotective and nephroprotective) effects (8,9). Although the relationship between renalase and kidney diseases is known, there are very few studies published to date on renalase levels in children. In their study, Skrzypczyk et al. (9) found a negative relationship between renalase level and glomerular filtration rate in children with glomerular kidney disease. They also revealed that renalase levels in patients with chronic kidney disease were significantly higher than their healthy controls (9).

In our study, we aimed to demonstrate the relationship between serum renalase levels and presence of renal scars in pediatric patients with recurrent urinary tract infection.

MATERIALS and METHODS

The study included 78 patients with recurrent UTI who were followed up in the Pediatric Nephrology Outpatient Clinic of the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, between July 2017 and June 2018. While 45 of the patients with recurrent UTI had renal scars, 33 had no scars. 20 healthy children of similar age and gender to the patient group were determined as the control group. Patients with accompanying systemic disease, active UTI, and chronic renal failure were not included in the study.

While blood tests were taken from the patients during their routine controls, 2 cc blood samples were taken to measure renalase levels and were centrifuged and stored at -80° C. All patients had voiding cystourethrographies and children with vesicoureteral reflux were recorded. Patients in the study group were grouped as normal, scarred, and atrophic kidney patients according to dimercaptosuccinic acid (DMSA) scintigraphy results. None of the patients whose renalase levels were measured had an active infection. The control group consisted of healthy children who applied to general pediatric outpatient clinics for various reasons. When blood was taken from these patients for any reason, an extra 2 cc blood sample was taken and centrifuged and reserved for renalase level testing. Renalase was studied using the ELISA (Sandwich ELISA) method with the "LifeSpan Biosciences Human Renalase, USA" kit in the microbiology laboratory of our hospital, with the Etimax 3000 microeliza device. Normal values were determined as 0.78-50 ng/ml, which the kit perceives as normal, and values below 0.78 ng/ml were determined to be lower than normal. Written consent was obtained from the patients' families to participate in the study. The study was approved by the Ethics Committee of Ankara Children's Health and Diseases Hospital (2017-088/14.06.2017).

Statistical evaluation of the data was performed using Statistical Package for the Social Sciences (SPSS Inc., Armonk, NY, IBM Corp., USA) for Windows version 20.0. In the analysis of quantitative data, compliance with normal distribution was examined with "Kolmogrov Simirnov" and "Shapiro-Wilk tests". In comparisons of two independent groups, the "Independent Samples t" test was used if it showed a normal distribution, and the "Mann-Whitney U" test was used if it did not. The data were examined at a 95% confidence level and the test was considered significant if the p value was less than 0.050.

RESULTS

The study included the 78 patients with a history of recurrent UTI (7 boys, 9.0%; 71 girls, 91.0%) and 20 healthy children (3 boys,

Table I: Evaluation of the relationship between Renal scar and VUR

	VUR n (%)		Total
	+	-	
Renal Scar + -	32 (71) 6 (18.2)	13 (29) 27 (81.8)	45 33
Total	38 (48.7)	40 (51.3)	78

Table II. Relationship between groups and Renalase level

	Renalase level (ng-ml) (mean±SD)	p
Recurrent UTIs group (n=78) Control group (n=20)	2.5±0.2 1.7±0.4	0.014
Renal scar + group (n=45) Scar-free group (n=33)	2.8±3.1 2.0±0.4	0.005

15%; 17 girls, 85%) . The mean age of the patients in recurrent UTI group and healthy controls were 11.71±0.91 years and 12.35±1.83 years, respectively. VUR was detected in 48.7% of patients (38/78) followed up with recurrent UTI. The most common stage 5 VUR (14.1%) was observed. While DMSA scintigraphy was reported normal in 42.3% of the patients (n=33), scars were detected in one kidney in 11 patients (14.1%) and in both kidneys in 6 patients (7.7%). Unilateral atrophic kidneys were detected in 28 (35.9%) patients. Of 45 recurrent UTI with renal scar, 32 (71%) also had VUR and of 33 recurrent UTI without renal scarring, 6 (18.2%) had VUR (Table I).

The renalase level of the recurrent UTI group was found to be significantly higher than the control group (p=0.014). However, renalase levels were within normal limits in both groups. Renalase level was found to have a significant relationship with renal scarring. The mean renalase level of the scar group was found to be significantly higher than the scar-free group (p=0.005) (Table II). It was found that there was no statistical difference between the renalase means of children with scars depending on whether they had VUR or not (p=0.688).

DISCUSSION

In our study, VUR was detected in 48.7% (38/78) of patients with recurrent UTI, and stage 5 VUR was the most common (14.1%). Known risk factors associated with recurrent UTI include have a grade 3–5 VUR and Voiding cystourethrographies are recommended to investigate VUR and other anatomical bladder defects in children with recurrent febrile UTI (10,11).

Renal scarring was detected in 57.6% (45/78) of our patients with recurrent UTI, and 71% (32/45) of patients with renal scar also had VUR. National Institute for Health and Care Excellence (NICE) guidelines recommend DMSA scans 4-12 months after acute infection to detect renal scars in children with recurrent UTI (12). VUR, which can be complicated by recurrent UTI, can cause chronic kidney damage and scarring (13). Approximately 40-60% of all children with a febrile UTI develop permanent renal scars (14).

Renalase is a monoamine oxidase that degrades catecholamines, mainly of renal origin but is also found in the heart, skeletal muscle, small intestine and liver. Three main factors determine the level of renalase in the blood: renal function, renal perfusion and serum catecholamine levels (15). Previous pediatric and adult studies have shown that renalase is negatively correlated with GFR and renalase levels increase in proportion to the deterioration of kidney functions (9,16). While Malyszko et al. (16), Zbroch et al. (17) and Skrzypczyk et al. (9) showed that renalase level increased in chronic kidney patients, Desir (18) suggested that renalase level decreased. Janusz et al.(19) also showed that renalase levels were significantly lower in children with solitary kidneys. The studies show that renalase production is primarily impaired in CKD patients and increases with disease progression (20). The increase in renalase levels in chronic kidney disease patients suggests a compensatory production in extrarenal organs, possibly in response to catecholamine excess, sympathetic nervous system activation, or oxidative stress, which are common in these patients (21). Skrzypczyk et al. (9) found that renalase was 59.45±23.25 µg /mL in children with chronic kidney disease and 27.20±5.15 µg /mL in the control group. Serum and urine renalase median levels in children with solitary functioning kidney was found, 23.07 µg/mL and 145.28 ng/mL, respectively in a study by Taranta-Janusz et al. (8) (Detection range was 3.12-200 ng/mL). No normal range or cutoff value is given for serum renalase. In our study, renalase levels were found to be significantly higher in patients with recurrent UTI (2.5±0.2 ng/mL) than in the control group (1.7±0.4), and in the renal scar group compared to the scar-free group. It was found that there was no statistical difference between the renalase means of children with renal scars depending on whether they had VUR or not. In line with our results, we consider increased renalase levels as a sign of increased renal scarring.

A study in cultured human kidney-2 cells showed that renalase removes TGF-β1-mediated renal tubular fibrosis by silencing the ERK1/2 MAPK activation pathway (22). Wu et al. (23) showed that in their recent study, renalase prevents renal fibrosis by preventing endoplasmic reticulum stress and down-regulating GSK-3β/SNAIL signaling. Wu et al. (22) in their study evaluating the therapeutic efficacy of renalase in rats with complete unilateral ureteral obstruction, they showed that renalase could improve renal interstitial fibrosis. Therefore, they stated that exogenous renalase supplementation may be an effective agent for slowing chronic kidney disease progression. But there are still no human studies on this subject (22). There are a limited number of studies examining the relationship between renalase and kidney diseases in children, and there are no studies in the literature investigating the relationship between renal scar and renelase. Renalase has been shown

to be a biomarker of chronic kidney disease and to alleviate renal necrosis, apoptosis, and inflammation. However, despite significant evidence for a relationship between renalase and renal pathophysiology, its precise role in renal physiology and pathology remains unclear due to conflicting study results (21).

More comprehensive studies are needed to determine the relationship between renalase and renal scarring and to answer the question of whether it can be used as an early marker of scarring. Additionally after clarifying the role of renalase in renal scarring, it might come up as a new agent to prevent fibrosis and scar development in patients with recurrent urinary tract infections.

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