

**DMSA AND VESICoureTERIC REFLUX DIAGNOSIS AND SIGNIFICANCE IN UTI IN CHILDREN FROM BARUCH PADEH PORIYA MEDICAL CENTER-ISRAEL**Haia Nasser<sup>1\*</sup>, Jerdev Michael<sup>2</sup>, Susan Nasser<sup>2</sup>, Sami Shehadeh<sup>3</sup>, Said Abozed<sup>3</sup> and Dr. Wael Nasser<sup>1</sup><sup>1</sup>Nephrology and Hypertension Division Baruch-Padeh Poriya Medical Center, Lower Galilee, Faculty of Medicine in Galilee, Bar Ilan University Israel.<sup>2</sup>Department Radiology Baruch Padeh Poriya Medical Center Lower Galilee.<sup>3</sup>Department of Pediatrics Baruch Padeh Poriya Medical Center Lower Galilee.**\*Corresponding Author: Haia Nasser**

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**ABSTRACT**

**Background and Objective:** Definitive diagnosis of vesicoureteral reflux (VUR) is by voiding cystourethrogram (VUCG), yet this is an uncomfortable procedure and does not detect renal scars. Technetium 99m Tc dimercaptosuccinic acid (DMSA) scintigraphy is currently the standard test for detecting renal scars. The aim of the current study was to examine the capability of urinary system ultrasonography (USG) and DSMA to distinguish VUR, and thus to replace VUCG. **Methods:** Analysis of medical records of children, from birth to age 9 years, with symptoms of urinary tract infection who underwent VUCG for detection of VUR at one medical center. **Results:** Of 88 children, 73 (83%) were girls, 72 (97%) had fever. VCUG detected VUR in 33 (38%). USG revealed abnormal findings in 44% (14/32) of the children with VUR and 41% (22/54) of those without VUR. Of the 36 children with abnormal findings on DSMA, 33% were without VUR and 24 (67%) with VUR: 8/24 (33%) had VUR grade 1-2 and 16/24 (67%) VUR grade 3-5. Of the 33 with normal DSMA findings 27 (82%) were without VUR and 6 (18%) with VUR: 4/6 (67%) had VUR grade 1-2 and 2 (33%) VUR grade 3-5. **Conclusions:** USG findings were not shown to distinguish VUR or to be associated with DMSA findings. DMSA does not appear as a means of replacing VCUG for the detection of VUR, since an abnormal DMSA occurred in almost one-third of children with UTI and without VUR.

**KEYWORDS:** Vesicoureteral reflux (VUR), voiding cystourethrogram (VUCG), dimercaptosuccinic acid (DMSA).

**INTRODUCTION**

About one third of children with urinary tract infection (UTI) have been found to have vesicoureteral reflux (VUR), 1-5 though some studies have challenged an association between the two conditions.<sup>6,7</sup> Regardless of the degree of association, the presence of UTI in children with VUR is considered to pose a risk for pyelonephritis, due to the passage of infected urine from the bladder into the upper urinary tract. Definitive diagnosis of VUR is by voiding cystourethrogram (VCUG), yet this is an uncomfortable procedure and does not detect renal scars. Renal scarring in childhood has been associated with hypertension, preeclampsia, and end stage renal disease in adulthood.<sup>8</sup> Technetium 99m Tc dimercaptosuccinic acid (DMSA) scintigraphy is currently the standard test for detecting renal scarring. The European Association of Urology, the European Society of Pediatric Urology, and the American Urological Association guidelines recommend performing urinary system ultrasonography (USG) and DMSA scintigraphy in patients who have high grade VUR, high creatinine levels and intercurrent

UTI, to determine the presence of renal dysplasia and acquired renal scar; and the performance of VCUG in case of renal involvement. This is targeted to reduce urethral catheterization and ionizing radiation of the gonads.<sup>9</sup> The main aim of the current study was to examine the capability of USG and DSMA to distinguish VUR, and thus to replace VUCG.

**Abbreviations****UTI:** urinary tract infection;**VUR:** vesicoureteral reflux;**VCUG:** voiding cystourethrogram;**DMSA:** dimercaptosuccinic acid;**USG:** ultrasonography**METHODS**

This is a retrospective study of children, from birth to age 9 years, with symptoms of UTI who underwent VCUG for detection of VUR at Poria Hospital in Tiberius, Israel during 2009-2013. Indications for performing VCUG were urinary tract infections,

recurrent infections, lack of improvement following antibiotic treatment, hydronephrosis on ultrasonography, a small or ectopic kidney, and clinical signs of upper urinary tract infection or pyelonephritis.

Children with congenital anatomical abnormalities were excluded from the analysis. Demographic and clinical data (sex, age, background diseases, previous surgery, UTI symptoms), laboratory tests (blood, urine, culture), and results of VCUG, USG and DMSA were accessed from the hospital medical records. According to hospital protocol, VCUG was performed within one month of the beginning of complaints, for children up to six months old; and after performing DMSA, for older children. DMSA was done 3-5 months after the presentation of acute UTI.

Data are presented by proportions and percentages.

## RESULTS

Of 98 children with symptoms of urinary tract infection who were referred for cystography, the 88 who performed the test comprised the cohort. Males comprised 14 (16%) and females 73 (83%); the sex of one child was not recorded. The cohort comprised 36 (41%) children under one year of age, 50 (57%) aged 1-9 years, and 2 children for whom ages were not known. According to bacterial cultures, 2 of the children with suspected UTI, did not have infections. Of the 74 children for whom data were available regarding UTI symptoms, 72 (97%) had fever, 1 (1%) had pain, 6 (8%) had pain during urination, 7 (9%) shaking, and 7% frequent urination. Of the 71 children for whom the location of the infection was known, 10 (14%) had infections in the lower urinary tract and 61 (86%) in the upper urinary tract.

Altogether, 33 (38%) of the children had VUR. Table 1 presents data according to the presence of VUR. Rates of VUR were 29% (4/14) among boys and 38% (28/73) among girls; 25% (9/36) among children under age one year and 48% (24/50) among children aged 1- 9 years; 29% of children with a first UTI and 49% of children with recurrent UTI; 50% (5/10) among children with infections of the lower urinary tract and 38% (23/61) among those with infections of the upper urinary tract.

Of the 86 (98%) who performed ultrasonography, abnormal findings were detected in 36 (42%) (Figure 1). Findings were abnormal in 44% (14/32) of the children with VUR and 41% (22/54) of those without VUR.

Of the 69 (78%) children who underwent DSMA, abnormal findings were detected in 36 (52%) (Figure 2). Of those with abnormal findings, 24 (67%) had VUR and 12 (33%) were without VUR. Of those with VUR, 8/24 (33%) had VUR grade 1-2 and 16/24 (67%) had VUR grade 3-5. Of the 33 with normal findings, 6 (18%) had VUR and 27 (82%) were without VUR. Of the 6 with VUR, 4 (67%) had VUR grade 1-2 and 2 (33%) had

VUR grade 3-5. Among children who underwent DSMA, abnormal findings were detected in 16/18 (89%) of children with VUR grade 3-5, 8/12 (67%) of those with VUR grade 1-2, and 12/39 (31%) of those without VUR (Figure 3).

## DISCUSSION

In this study of children who were symptomatic for UTI, VCUG detected VUR in 38%. This is similar to rates of 31-39% reported in other studies,<sup>2-5</sup> and compares with 17% among children without UTI.<sup>2</sup> However, an Israeli study of children aged 0-5 years (mean age 11 months), with uncomplicated febrile UTI, reported VUR in 18% (47/255). VUR may be more prevalent than thought, as it is generally only tested among individuals with UTI. The demonstration of similar rates of VUR among groups of children whose urine samples showed certain or improbable UTI,<sup>6</sup> as well as among children with proven or false UTI,<sup>7</sup> counters a relationship between UTI and VUR, and indicates higher rates of VUR also among those without UTI.

We report that 73% of children with VUR had abnormal DSMA. Our findings support studies that reported increased prevalence of abnormal DMSA findings among patients with VUR compared to those without VUR;<sup>3,5, 10-15</sup> and contrast with studies that reported no increased risk of abnormal DMSA in patients with VUR.<sup>16-18</sup> Nevertheless, the observation of abnormal findings on DMSA in almost one-third of our cohort of children with UTI and without VUR, concurs with others who reported renal scarring without the presence of VUR;<sup>10,19,20</sup> and supports the increasingly popular view that VUR is not a good predictor of renal scarring,<sup>21-23</sup> nor of UTI recurrence. Thus, a correlation between VUR and renal scars does not indicate that treatment of VURs protects against renal scars.<sup>6</sup> The findings from the current and other studies raise questions regarding the performance of VCUG to diagnose VUR. In a British study, the rate of scars halved and the presence of VUR without scarring increased 12 times, during a period in which more children were treated earlier for UTI,<sup>24</sup> supporting prompt treatment of UTI, regardless of the presence of VUR, as the approach to avoiding renal scars.

Of those with normal DMSA in the current study, only 18% had VUR, including only 6% with VUR grade 3-5. We report abnormal DSMA in 2.2 times as many children with VUR grades 1-2 as without VUR (66.7% vs. 30.8%) and in 2.9 times as many with VUR 3-5 as without VUR (88.9% vs. 30.8%). The implication is that a normal DMSA test confers a high chance of the absence of VUR, and particularly of high grade VUR. A number of studies have suggested that normal DMSA findings may be a good predictor of the absence of VUR.<sup>4,11</sup> Conversely, greater risk of kidney damage has been shown in patients with higher grade of VUR.<sup>25-30</sup> A prospective study of 565 children reported renal scars in 43% of those with VUR grades 4-5.<sup>30</sup>

In the current study, USG did not distinguish VUR; similar rates of abnormal findings were detected among children with normal and abnormal ultrasound findings. Another Israeli study showed questionable yield of renal ultrasound in detecting VUR, with particularly low sensitivity.<sup>31</sup> Two prospective studies have shown better sensitivity of DMSA than ultrasonography in the detection of VUR, in Iranian children, mean age 38 months<sup>4</sup> and in Thai children less than one year old.<sup>32</sup>

The current cohort of patients with symptomatic UTI comprised more than 5 times the number of girls as boys; 41% were under one year old. Rates of VUR were higher among girls than boys: 38% and 29% respectively, concurring with other studies.<sup>33</sup>

This study has a number of limitations, particularly due to the retrospective design. Data were missing and not all patients underwent all tests investigated. More patients without VUR than with VUR did not undergo DMSA (29% compared to 5%).

Our findings show an increased risk of renal scars in children with VUR, and particularly those with high grade DMSA. However, since almost one-third of children with normal DMSA results had VUR, DMSA does not appear as a means of replacing VCUG for the detection of VUR. Neither do our findings support the importance of detecting VUR, since 31% of children without VUR had abnormal DMSA results. Further reasons for questioning the importance of detecting VUR is its tendency to spontaneous resolution, and the evidence that it may be common also among children who do not present with UTI. VCUG is an unpleasant test that yields results of uncertain clinical implication. Renal scars, rather than VUR, are the more important clinical finding. However, DMSA is a costly procedure, and its results and interpretation vary among clinics, due to the use of different isotopes.<sup>34</sup> Moreover, DSMA was shown to confer a 1.3-fold higher radiation dose than continuous fluoroscopy voiding VCUG, a 10-fold higher radiation dose than pulsed fluoroscopy VCUG, and a 200-fold higher radiation dose than radionuclide VCUG.<sup>35</sup>

**Table 1: Patient characteristics according to VUR presence.**

Characteristic	VUR (row percentiles)	No VUR (row percentiles)	Total (column percentiles)
Gender			
Males	4/14 (29%)	10/14 (71%)	14 (16%)
Females	28/73 (38%)	45/73 (62%)	73 (83%)
Unknown	1	0	1 (1%)
Age			
<1 year	9/36 (25%)	27/36 (75%)	36 (41%)
1-9 years	24/50 (48%)	26/50 (52%)	50 (57%)
Unknown			2 (2%)
Presence of UTI			
No UTI	1	1	2 (2%)
First UTI	9 (29%)	22 (71%)	31 (35%)
Recurrent UTI	22 (49%)	23 (51%)	45 (51%)
Unknown	1	9	10 (11%)
Infection location			
Lower urinary tract	5 (50%)	5 (50%)	10 (11%)
Upper urinary tract	23 (38%)	38 (62%)	61 (69%)
Unknown	5	12	17 (19%)
Infection type			
Pyelonephritis	24 (42%)	33 (58%)	57 (65%)
Nephronia	6 (38%)	10 (62%)	16 (18%)
Cystitis	1 (33%)	2 (67%)	3 (3%)
Unknown	2 (17%)	10 (83%)	12 (14%)

Figure 1: Ultrasound findings according to VUR

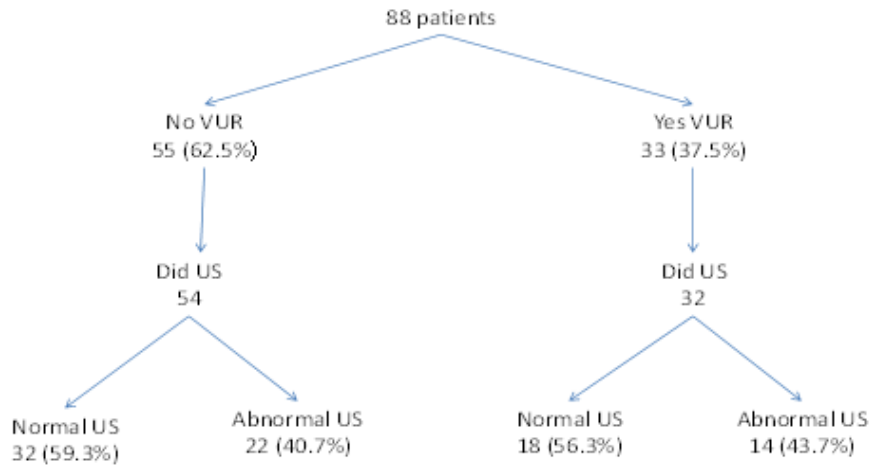


Figure 2: VUR presence and level according to DSMA

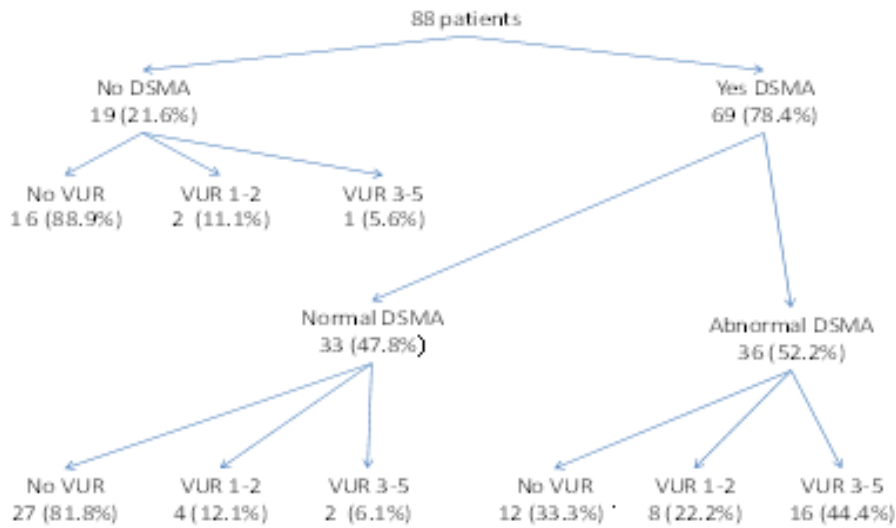
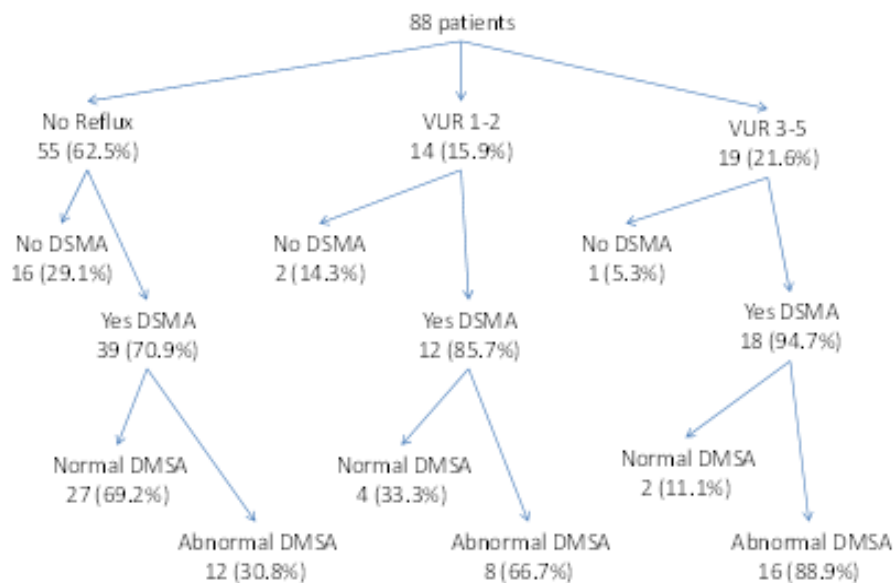


Figure 3: DSMA findings according to VUR presence and level



## CONCLUSION

This study did not find urinary system ultrasonography to distinguish VUR, nor to be associated with DMSA findings. DMSA did not demonstrate capability of replacing VCUG for the detection of VUR. However, the importance of predicting VUR was not supported, since almost one-third of children without VUR had abnormal DMSA results.

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