

The Relation of Vesicoureteral Reflux and Renal Scarring in Childhood Urinary Tract Infection

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Objective: Assess the relation of age and sex in vesico ureteral reflux (VUR) and renal scarring and the relation of VUR and renal scarring in childhood urinary tract infection.

Material and Method: A descriptive study of one hundred and twenty-six children who received renal cortical scintigraphy from 1st Jan 2000 to 31st Dec 2004 in the Department of Radiology, Faculty of Medicine Siriraj Hospital, was conducted. Ninety-three (50 males, 43 females) patients were diagnosed with urinary tract infections (UTIs) but only ninety-one of them had renal cortical scintigraphic results available. The male to female ratio was 1.16:1. The mean age of the patients was 4.33 years (SD = 4.17, range 7 days - 16 years). During the 1st year of life the male to female ratio is 2.6:1. Fever, dysuria, and poor feeding were the most presenting signs and symptoms. Eighty-five (45 males, 40 females) patients received Voiding Cysto Urethro Gram (VCUG).

Result: The authors did not find the correlation between the age groups and sex with VCUG results on right and left side, respectively ($p = 0.856$, $p = 0.145$, $p = 0.77$, $p = 0.75$). Ninety-one (49 males, 42 females) patients received DMSA renal scintigraphy. Fifty-two patients (57.1%) had abnormal DMSA renal scan results. However, the authors did not find the correlation between age groups and sex with DMSA renal scan results on the right and left kidneys, respectively. ($p = 0.202$, $p = 0.416$, $p = 0.511$, $p = 0.791$). The authors compared times of UTIs with and DMSA renal scintigraphy in each side of the kidney. Even though the authors did find the correlation between episodes of UTIs and abnormal DMSA on the left kidneys ($p = 0.017$), it was not found on the right kidneys ($p = 0.081$). There were 80 patients who received both VCUG and DMSA renal scintigraphy. The authors found the correlation between severity of VUR and abnormal DMSA results on right and left kidneys ($p = 0.001$, $p = 0.01$).

Conclusion: The authors recommend that all children who have repeated UTI and/or VUR, irrespective of age and sex, should receive DMSA renal scintigraphy to detect renal scarring and follow up future complications.

Keywords: Urinary tract infection, Renal cortical scintigraphy, Renal scarring

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Urinary tract infections (UTIs) are common in children. Approximately 3% of girls and 1% of boys are diagnosed as UTIs. Most UTIs occur during the 1st year of life and male preponderance with the male:female ratio of 2.8-5.4:1. Beyond 1-2 years, the male:female ratio is 1:10. UTIs are much more common in uncircumcised boys⁽¹⁾.

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UTI that involves the renal parenchyma, termed acute pyelonephritis, may result in renal scarring or permanent renal damage, which may lead to hypertension, hyposthenuria, proteinuria, complications during pregnancy, and even renal failure⁽²⁾. Recurrent infections, vesico ureteral reflux (VUR) and renal scarring are major risk factors for the development of renal damage^(3,4). Early diagnosis and treatment may prevent or decrease renal damage caused by acute febrile UTI⁽⁵⁾.

Renal cortical scintigraphy with technetium-99m labeled Di Mercapto Succinic Acid (DMSA) is considered to be the most sensitive technique compared with intravenous pyelography (IVP) and ultrasonogram for detection of renal parenchymal change in acute pyelonephritis and renal scarring. The pathological changes of VUR and post-pyelonephritic renal scarring have been studied both in animal and human kidneys^(6,7). It is generally believed that the risk of renal scarring after pyelonephritis is low in children over the age of 5 years and without VUR. The goal of this retrospective study was to assess the relationship of age and sex in VUR and renal scarring as well as the relationship of VUR and renal scarring in childhood urinary tract infection.

Material and Method

A retrospective and descriptive study of 126 patients who received DMSA renal scintigraphy in the Department of Radiology, Faculty of Medicine Siriraj Hospital from January 1, 2000 through December 31, 2004. Ninety-three of these were diagnosed as UTIs but only ninety-one patients had DMSA renal scintigraphic result available. Infection was defined by growth of at least 10⁵ colony-forming units per milliliter of a single bacterial species from midstream or catheter specimens. Data on the following items were analyzed: age groups, sex, presenting symptoms, episodes of UTIs, voiding cystourethrogram (VCUG) results, and DMSA renal scintigraphic results.

VCUG was used for detection and grading of VUR. VUR was graded as follows: Grade I reflux was defined as reflux into the ureter; grade II was reflux into a non-dilated collecting system; grade III was reflux into a mildly dilated collecting system; grade IV was reflux into a moderately dilated collecting system; and grade V was reflux into a severely dilated collecting system.

Renal scintigraphy was performed 3 to 6 months after the last UTI with a gamma camera equipped with a low-energy, high-resolution collimator 2-3 hours following intravenous injection of a dose of 99m Technetium dimercaptosuccinic acid or 99mTc DMSA, according to the recommendations of the European Association of Nuclear Medicine⁽⁸⁾. One posterior and two posterior oblique views were obtained for 700,000 counts each with a matrix size of 256x256. The relative uptake function of both kidneys was calculated as percentage renal uptake of each kidney. Image interpretation was assessed in terms of renal size, relative uptake function, uniformity of renal uptake, with single

or multiple cortical defects, and associated contraction or volume loss in the involved cortex⁽⁹⁾.

Statistical analysis

Results are expressed as mean \pm SD. Clinical parameters of the following items : age groups, sex, times of UTIs, VCUG results, and DMSA renal scintigraphic results, were analyzed with a chi-squared test. Statistical significance was set at p value of less than 0.05. SPSS statistical package (version 11.0) was used.

Results

Ninety-three patients with UTIs, 50 (53.8%) males and 43 (46.2%) females, aged 7 days-16.42 years (mean 4.33 \pm 4.17 years) received DMSA renal scintigraphy but results were not available in two patients. Ratio of male and female was 1.16:1. In patients less than five years of age, males had more chance to receive DMSA renal scintigraphy whereas in patients more than five years of age, females had more chance to receive it (Table 1). Fever (87.1%) was the most presenting sign and symptom that brought patients to the physician's attention. Dysuria (12.9%) and poor feeding (12.9%) were the second most presenting signs and symptoms. Other signs and symptoms were turbid urine, abdominal pain, frequent voiding, lethargy and gastrointestinal symptoms.

Eighty-five patients received VCUG. Fifty patients were excluded from the present study due to posterior urethral valves and neurogenic bladder. There were 44 (55%) males and 36 (45%) females. Of these 80 patients, there were 25 (31.3%) unilateral VUR and 29 (36.3%) bilateral VUR. The authors divided the patients into three age groups, \leq 1 year, > 1-5 years, and > 5 years. In the age group \leq 1 year, VCUG showed equal VUR of 42.3% on right and left sides, whereas in the age group > 1-5 years and > 5 years, VCUG showed more VUR on the left side than VUR on the right side.

Table 1. Age groups by sex (N = 93)

	Sex		
	Male	Female	Total
Age- group			
\leq 1 yr	21 (72.4%)	8 (27.6%)	29 (31.2%)
> 1-5 yr	18 (54.5%)	15 (45.5%)	33 (35.5%)
> 5 yr	11 (35.5%)	20 (64.5%)	31 (33.3%)
Total	50 (53.8%)	43 (46.2%)	93 (100%)

However, the authors did not find the correlation between age groups and sex with VCUG results on right and left sides, respectively ($p = 0.856$, $p = 0.145$, $p = 0.77$, $p = 0.75$) (Table 2).

Ninety-one patients, 49 (53.9%) males and 42 (46.1%) females, received DMSA renal scintigraphy. Four patients had left solitary kidneys, so there were 87 right and 91 left kidney units. Fifty-two patients (57.1%) had abnormal DMSA renal scan results. Eleven of those had bilaterally abnormal DMSA renal scan. In

the age group ≤ 1 year and $> 1-5$ years, there were more abnormal DMSA renal scans on the left kidneys than abnormal DMSA renal scan on the right kidneys, whereas in the age group > 5 years, there were opposite results. However, the authors did not find the correlation between age groups and sex with DMSA results on the right and left kidneys, respectively ($p = 0.202$, $p = 0.416$, $p = 0.511$, $p = 0.791$) (Table 3).

The authors compared episodes of UTIs with and DMSA renal scintigraphy in each side of the

Table 2. Correlation of age groups, sex and VCUG results (N = 80)

	VCUG on right sides			VCUG on left sides		
	VUR	No VUR	Total	VUR	No VUR	Total
Age group						
≤ 1 yr	11 (42.3%)	15 (57.7%)	26 (100%)	11 (42.3%)	15 (57.7%)	26 (100%)
$> 1-5$ yr	13 (46.4%)	15 (53.6%)	28 (100%)	19 (67.9%)	9 (32.1%)	28 (100%)
> 5 yr	13 (50%)	13 (50%)	26 (100%)	16 (61.5%)	10 (38.5%)	26 (100%)
Total	37 (46.3%)	43 (53.8%)	80 (100%)	46 (57.5%)	34 (42.5%)	80 (100%)
Sex						
Male	21 (47.7%)	23 (52.3%)	44 (100%)	26 (59.1%)	18 (40.9%)	44 (100%)
Female	16 (44.4%)	20 (55.6%)	36 (100%)	20 (55.6%)	16 (44.4%)	36 (100%)
Total	37 (46.3%)	43 (53.8%)	80 (100%)	46 (57.5%)	34 (42.5%)	80 (100%)

Age group and VCUG on right and left sides; Chi-square test ($p = 0.856$) and ($p = 0.145$)

Sex and VCUG on right and left sides; Chi-square test ($p = 0.77$) and ($p = 0.75$)

Table 3. Correlation of age groups, sex and DMSA renal scintigraphic results

	DMSA on right kidneys (N = 87)			DMSA on left kidneys (N = 91)		
	normal	abnormal	Total	normal	abnormal	Total
Age group						
≤ 1 yr	20 (80%)	5 (20%)	25 (100%)	18 (66.7%)	9 (33.3%)	27 (100%)
$> 1-5$ yr	22 (71%)	9 (29%)	31 (100%)	17 (51.5%)	16 (48.5%)	33 (100%)
> 5 yr	18 (58.1%)	13 (41.9%)	31 (100%)	20 (64.5%)	11 (35.5%)	31 (100%)
Total	60 (69%)	27 (31%)	87 (100%)	55 (60.4%)	36 (39.6%)	91 (100%)
Sex						
Male	31 (66%)	16 (34%)	47 (100%)	29 (59.2%)	20 (40.8%)	49 (100%)
Female	29 (72.5%)	11 (27.5%)	40 (100%)	26 (61.9%)	16 (38.1%)	42 (100%)
Total	60 (69%)	27 (31%)	87 (100%)	55 (60.4%)	36 (39.6%)	91 (100%)

Age group vs DMSA on right and left kidneys; Chi-square test ($p = 0.202$) and ($p = 0.416$)

Sex vs DMSA on right and left kidneys; Chi-square test ($p = 0.511$) and ($p = 0.791$)

kidney. Four patients did not have data about episodes of UTIs. There were 30.1% and 39.1% of abnormal DMSA renal scans on the right and left kidneys, respectively. In the first UTI, there were more abnormal DMSA renal scans on the left kidneys than the right kidneys. Even though the authors did find correlation between episodes of UTIs and abnormal DMSA on the left kidneys ($p = 0.017$), the authors did not find correlation between them on the right kidneys ($p = 0.081$) (Table 4).

VCUG results in each side of kidneys were groups as normal, VUR grade I-III, and VUR grade IV-V. Eighty patients received both VCUG and DMSA renal scintigraphy. Four patients had left solitary kidneys. Three of them had abnormal DMSA results. There were 9 (11.3%) and 40 (50%) patients with bilaterally and unilaterally abnormal DMSA renal scan results. The authors compared VCUG results and DMSA renal scintigraphy in each side of the kidney. The authors did find the correlation between severity of VUR and

abnormal DMSA renal scan results on each side of the kidneys ($p = 0.001$, $p = 0.01$) (Table 5).

Discussion

It has been generally believed that young children are more prone to development of renal scarring after pyelonephritis than patients over 5 years old. This has led to differences in investigations and treatment according to age. The presented data did not confirm this belief. The authors did not find the correlation between age groups and sex with VCUG or DMSA renal scan results. Lavocat et al⁽¹⁰⁾ also demonstrated that the age of patients did not have any effects on the severity of the initial renal involvement or on the evolution of the cortical scintigraphic abnormalities. Moreover, the data from Orellana et al⁽¹¹⁾ went against conventional belief. The group found that children older than 1 year developed more renal scarring after pyelonephritis than those younger than 1 year (70.1% vs 36.4%; $p < 0.0001$).

Table 4. Correlation of episodes of UTI and DMSA renal scintigraphic results

	DMSA on right kidneys* (N = 83)			DMSA on left kidneys** (N = 87)		
	normal	abnormal	Total	normal	abnormal	Total
Episodes of UTI						
1	21 (87.5%)	3 (12.5%)	24 (100%)	18 (72%)	7 (28%)	25 (100%)
2	21 (61.8%)	13 (38.2%)	34 (100%)	24 (70.6%)	10 (29.4%)	34 (100%)
> 3	16 (64%)	9 (36%)	25 (100%)	11 (39.3%)	17 (60.7%)	28 (100%)
Total	58 (69.9%)	25 (30.1%)	83 (100%)	53 (60.9%)	34 (39.1%)	87 (100%)

* Chi-square test ($p = 0.081$)

** Chi-square test ($p = 0.017$)

Table 5. Correlation of VCUG and DMSA renal scintigraphic results

	DMSA on right kidneys* (N = 76)			DMSA on left kidneys** (N = 80)		
	normal	abnormal	Total	normal	abnormal	Total
VCUG on right sides				VCUG on left sides		
normal	32 (80%)	8 (20%)	40 (100%)	26 (76.5%)	8 (23.5%)	34 (100%)
VUR grade I-III	16 (76.2%)	5 (23.8%)	21 (100%)	13 (54.2%)	11 (45.8%)	24 (100%)
VUR grade IV-V	4 (26.7%)	11(73.3%)	15 (100%)	8 (36.4%)	14 (63.6%)	22 (100%)
Total	52 (68.4%)	24 (31.6%)	76 (100%)	47 (58.8%)	33 (41.3%)	80 (100%)

* Chi-square test ($p = 0.001$)

** Chi-square test ($p = 0.01$)

For the diagnosis of renal scarring, it is important to consider the timing of DMSA renal scintigraphy. Because of limitation of DMSA renal scintigraphy in distinguishing acute pyelonephritis from renal scarring, a reversible defect from acute pyelonephritis could be falsely labeled as permanent renal scar. The ideal time for visualizing renal scarring at DMSA scan has not yet been established. A delay of at least 3 months or up to 5 months after infection has been suggested⁽¹²⁻¹⁴⁾. But some experts have suggested as long as 6 or 12 months^(10,15-17). The study from Zaki M et al⁽¹⁸⁾ on follow-up DMSA renal scintigraphy at 6 months after diagnosis found DMSA results returned to normal in 56%, improved with residual renal abnormality in 6%, and persisted renal parenchymal defects in 38%. Fifty-seven percent of the presented patients with UTIs had renal lesions at 3-6 months after UTIs on DMSA renal scintigraphy. The data were close to 59% which was previously reported in Thailand⁽¹⁹⁾. There was a wide range of renal scarring prevalence in different countries such as Ireland (59%), Taiwan (57%), Kuwait (44%), Sweden (38%), Hong Kong (37%), Australia (24%), and the United States of America (15%)^(15,16,20,21,18,22,23). However, such a high percentage of renal lesions in the presented data (57.1%) could reflect the retrospective nature and timing of DMSA renal scintigraphy. With high percentage of VUR (67.5%) in the presented patients, they probably had a tendency to receive DMSA renal scintigraphy, whereas another report in Thailand had VUR of only 19% of patients⁽²⁴⁾.

The correlation between episodes of UTI and renal scarring was seen in the present study. However, the difference was statistically significant only on the left side of kidneys. This could be a reflection of the number of the presented patients in the present study. Loutfi et al⁽²⁵⁾ demonstrated that the yield of abnormal DMSA renal scan in the first episode of UTI (42%) and in recurrent UTI (55%) was not statistically significant. However, the data from Orellana et al⁽¹¹⁾ showed that there was more permanent renal damage in children with recurrent UTI than in those with a first episode of UTI (72.6% vs 55.9%; $p = 0.004$).

The correlation between severity of VUR and renal scarring has been shown in several studies^(11,14,22,26-28). This correlation was confirmed in the present study. Camacho et al⁽²⁶⁾ found that children with abnormal DMSA had a higher chance of VUR than children with normal DMSA (48% vs 12%). Hoberman et al⁽¹⁵⁾ also found renal scarring was more likely to occur in children with VUR than in those without VUR (14.7% vs 6%, $p = 0.03$). Goldman et al⁽²⁹⁾ observed that

abnormal DMSA renal scan was found only in patients with VUR grade 3 and above. However a study from Ataei et al⁽³⁰⁾ showed that the frequency of abnormal DMSA renal scan in the presence of VUR and in non-refluxing renal units did not differ (71.4% vs 72.2%, $p > 0.05$). Interestingly, 20% of normal VCUG on the right sides had abnormal DMSA renal scan on the right kidneys and 23.5% of normal VCUG on left sides had abnormal DMSA renal scan on left kidneys. A large portion of patients with renal scarring in the absence of demonstrable reflux suggests that other mechanism, such as bacterial adherence, may play a role for bacterial transportation to the kidney⁽³¹⁾.

Conclusion

Older children have a risk of permanent renal damage as much as younger children. The present study confirmed that recurrent UTI and VUR had good correlation with renal scarring on DMSA renal scintigraphy. The authors recommend that all children who had recurrent UTI and/or VUR, irrespective of age and sex, will benefit from DMSA renal scintigraphy to detect permanent renal scarring. Prospective study is needed for more complete data to associate renal scarring with prognosis and outcome.

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ความสัมพันธ์ของภาวะปัสสาวะไหลย้อนและแผลที่ไตในผู้ป่วยเด็กทางเดินปัสสาวะอักเสบ

สุโรจน์ ศุภเวคิน, ขนิษฐา คูศิริไลส์, เสาวลักษณ์ สุนนางกูร, จิราพร ศรีประภาภรณ์, อนิรุธ ภัทรากาญจน์,
อัจฉรา สัมบุญณานนท์

การศึกษาย้อนหลังในผู้ป่วยเด็ก 126 รายที่ได้รับการตรวจ DMSA renal scan ระหว่างวันที่ 1 มกราคม พ.ศ. 2543 ถึง 31 ธันวาคม พ.ศ. 2547 ที่ภาควิชารังสีวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล โดยเป็นผู้ป่วยทางเดินปัสสาวะอักเสบติดเพื่อจำนวน 93 ราย ในจำนวนนี้มีข้อมูลการตรวจ DMSA 91 ราย อัตราส่วนเพศชาย : เพศหญิง = 1.16 : 1 ค่าเฉลี่ยอายุ 4 ปี 4 เดือน \pm 4 ปี 2 เดือน (ช่วงอายุตั้งแต่ 7 วัน ถึง 16 ปี) พบว่าอัตราส่วน ในช่วงขวบปีแรก เพศชาย : เพศหญิง = 2.6 : 1 อาการแสดงที่ผู้ป่วยมาพบแพทย์ที่บ่อยที่สุด ประกอบด้วย อาการไข้ ปัสสาวะแสบขัด กินได้น้อยลง มีผู้ป่วยได้รับการตรวจ Voiding cystourethrogram (VCUG) 85 ราย การศึกษาไม่พบความสัมพันธ์ของ กลุ่มอายุ เพศกับผล VCUG ทั้งข้างขวาและซ้าย ($p = 0.856$, $p = 0.145$, $p = 0.77$, $p = 0.75$) ผู้ป่วยที่ได้รับการตรวจ DMSA renal scan มี 91 ราย โดยพบความผิดปกติในผู้ป่วย 52 ราย (57.1%) การศึกษาไม่พบความสัมพันธ์ของ กลุ่มอายุ เพศกับผล DMSA renal scan ทั้งข้างขวาและซ้าย ($p = 0.202$, $p = 0.416$, $p = 0.511$, $p = 0.791$) เมื่อเปรียบเทียบจำนวนครั้งของทางเดินปัสสาวะอักเสบกับผลของ DMSA renal scan ในไตแต่ละข้าง การศึกษาพบความสัมพันธ์ดังกล่าวในไตข้างซ้าย ($p = 0.017$) โดยไม่พบในไตข้างขวา ($p = 0.081$) มีผู้ป่วยที่ได้รับการตรวจทั้ง VCUG และ DMSA renal scan 80 ราย พบความรุนแรงของ VUR มีความสัมพันธ์กับการเกิดความผิดปกติของ DMSA renal scan ในไตข้างขวาและซ้าย ($p = 0.001$, $p = 0.01$) ผู้ศึกษามีความเห็นว่ามีผู้ป่วยเด็กทุกรายที่มีทางเดินปัสสาวะอักเสบติดเชื้อซ้ำและหรือมีปัสสาวะไหลย้อนสมควรส่งตรวจ DMSA renal scan เพื่อวินิจฉัยแผลเป็นในไตและการตรวจติดตามภาวะแทรกซ้อนที่อาจเกิดขึ้นตามมาได้ในภายหลัง