

## Vesico-Ureteral Reflux and Reflux Nephropathy in Children with Recurrent Urinary Tract Infection

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**ABSTRACT** We reviewed clinical and laboratory findings of patients with recurrent urinary tract infections (UTI) to detect the presence of vesico-ureteral reflux (VUR) or reflux nephropathy (RN). Only patients with evidence of more than 2 bouts of UTI's treated at the Department of Child Health, Cipto Mangunkusumo Hospital during the period from October 1, 1992 to September 30, 1993 were studied. There were 30 patients (15 boys, 15 girls) ranging in age from 2 months to 16 years (mean age = 5.5 years). RN as detected on dimercaptosuccinic acid (DMSA) scanning was found in 21 patients (12 unilateral, 9 bilateral). Mictiocyctourography (MCU) was done in 22 patients, revealing VUR in 14 patients, 10 of them showed renal scarring on DMSA scanning. Most of the patients has the duration of illness of less than 2 years. Clinical symptoms and signs (hypertension, proteinuria, increased plasma urea / creatinine) alone or in combination were more commonly found in patients with RN than in those without RN. The high prevalence of VUR and RN in patients with recurrent UTI in our series (63% and 70%, respectively), should draw our attention to detect UTI in its earliest stage, to be able to treat the patient promptly in order to prevent RN which eventually progresses into renal failure. [*Paediatr Indones* 1996;36:239-247]

### Introduction

Urinary tract infection (UTI) is important because the disease is frequently found in children. Recurrent UTI is usually found in children with predisposing factors, either as anatomical or functional lesion of urinary tract leading to urinary stasis or reflux. The presence of recurrent UTI in infants or toddlers is a clue for the possibility of

vesicoureteral reflux (VUR). Infected VUR can cause renal scarring; the higher the infection rate, the higher rate of the possibility of scar formation. The presence of cortical scarring and calyceal clubbing in association with vesicoureteral reflux is called as reflux nephropathy (RN); formerly known as chronic non obstructive atrophic pyelonephritis.

Many reports state that chronic pyelonephritis, especially those due to obstructive uropathy and reflux nephropathy, are the second cause of chronic renal failure in children.<sup>1,2</sup> The main problem in the prevention of renal failure caused by reflux nephropathy is the vagueness of clinical presentations of the disease especially in patients without the symptoms of urinary infection. Once the disease progresses to nephropathy, sooner or later renal failure will threaten. Therefore the only hope for the prevention is early detection and proper management of VUR and prompt treatment of any subsequent urinary infection before renal scarring develops. For this reason, early identification of renal scarring is necessary. Intravenous pyelography (IVP) is usually considered sufficient to detect renal scarring, but with Tc-99 m Dimercaptosuccinic acid (DMSA), the diagnosis of RN is more accurate. Renal scarring can be identified as a photon-deficient pattern or low emission area on the scan.<sup>3</sup> The aim of this study is to establish the prevalence of RN in children with UTI especially those patients with recurrent infection. From this finding we hope that our understanding about the outcome of VUR in children will increase.

## Methods

This study was designed descriptively using primary data recorded in a special form. The subjects were composed of patients with recurrent urinary tract infection either treated ambulatory or hospitalized at the Pediatric Ward Cipto Mangunkusumo Hospital from October 1, 1992 to September 30, 1993. Only those patients who had been infected more than twice were enrolled in this study. The clinical data consisted of age, sex, clinical symptoms and signs of UTI, blood pressure, urinalysis and renal function were recorded. Imaging procedures, including mictiocyctourethrogram (MCU), ultrasonography and intravenous pyelography (IVP) were conducted after medical treatment was accomplished. The gradation of reflux followed to the classification of International Reflux Study in Children.<sup>4</sup> Radionuclide scanning using Tc-99 m dimercaptosuccinic acid (Tc-99 m DMSA) was done at the Subdivision of Nuclear Medicine, Department of Radiology, Cipto Mangunkusumo Hospital, Jakarta. Scarred kidney are identified as polar, focal, or diffuse pattern on scintigraphy. For the purpose of the clinical and laboratory evaluations some definitions that relevant to the study were listed as follows:

- Hypertension in children was defined when either systolic or diastolic blood pressure is greater than 95th percentile for age, according to the report of the Task

Force on Blood Pressure Control in Children, 1977<sup>5</sup>

- Proteinuria was measured qualitatively using standard procedure of urine examination. The presence of protein ++ or more were recorded as proteinuria.
- Plasma urea and creatinine were termed as increasing when their values are greater than normal limits for age

## Results

During one year period (from October 1, 1992 to September 30, 1993) there were 32 patients who fulfilled the inclusion criteria, but two patients out of them were excluded from the study due to incomplete data. The remaining 30 patients were eligible for analysis. The age and sex distribution was shown in Table 2; there were 15 boys and 15 girls ranging in age from 2 months to 16 years with the mean of 5.5 years. The peak incidence of recurrent urinary tract infection was found in the age group of 5-12 years. Similarly, the peak prevalence of reflux nephropathy (RN) was also noted in this age group.

Table 1. Age and sex distribution of patients with reflux nephropathy

Age (yr)	Sex		Total	DMSA Scintigraphy		
	M	f		RN +	RN -	Total
0 -	2	3	5	3	2	5
2 -	3	3	6	5	1	6
5 -	7	8	15	10	5	15
≥ 12	3	1	4	3	1	4
Total	15	15	30	21	9	30
Mean age (years)				5.5	6.7	5.9

Abbreviations: DMSA = dimercaptosuccinic acid; RN = reflux nephropathy.

Renal scintigraphy using Tc-99 m DMSA was performed in all patients, but MCU was only done in 22 patients. The results of MCU and DMSA scanning were shown in Table 2. The sign of reflux nephropathy (RN) as shown by the presence of cortical scarring on DMSA scanning, was detected in 21 patients (70%), 12 patients of them with unilateral scarring and 9 patients with bilateral scarring. MCU done in 22 patients revealed that vesicoureteral reflux (VUR) were detected in 14 patients (64%), 10 out of them with renal scarring (71%) while in the remaining 4 patients, scarring were not identified. Four out of eight patients without reflux showed renal scarring while the

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remaining 4 patients did not show any scar formation. In those patients who showed the presence of reflux and scarring together, the site of reflux were precisely identical (comparable) with the location of renal scarring identified by DMSA scanning, i.e., 3 patients on the left kidney, 4 patients on the right, and 3 patients bilaterally.

Table 2. Results of mictiocyctourethrogram and DMSA scintigraphy

MCU	DMSA scintigraphy				
	RN + (n=21)			RN - (n=9)	Total (n=30)
	Left	Right	Bilateral		
VUR +	▪ Left	3		2	5
	▪ Right		4	1	5
	▪ Bilateral			3	4
VUR -		2	2	4	8
MCU not done	1	2	4	1	8

Abbreviations: MCU = mictiocyctourethrogram; DMSA = dimercoptosuccinic acid; RN = reflux nephropathy; VUR=vesico-ureteral-reflux.

Table 3. Duration of illness and reflux nephropathy

Duration of illness (yr)	DMSA SCINTIGRAPHY		
	Reflux nephropathy		
	+	-	
0-	12	2	14
2 - 4	6	2	8
> 4	3	5	8
<b>Total</b>	<b>21</b>	<b>9</b>	<b>30</b>
<b>Mean</b>	<b>1.95</b>	<b>4.55</b>	

The duration of illness as shown in Table 3 revealed that 14 patients (47%) had suffered from urinary infection for less than 2 years, 8 patients between 2 to 4 years and the rest 8 patients for more than 4 years. Of 21 patients with RN, 12 patients (57%) detected with the duration of illness less than 2 years, 6 patients between 2-4 years,

and the remaining 3 patients with more than 4 years period of illness, while in the group of non scarring 5 out of 9 patients has suffered from infection for more than 4 years.

Table 4 shows the correlation between clinical symptoms and signs of RN and the presence of renal scarring. The clinical signs of hypertension, proteinuria, and increased plasma urea and creatinine content either as a single sign or in combination were noted in 17 out of 21 patients with RN, the rest 4 were asymptomatic.

Table 4. Correlation between clinical signs and symptoms and the result of renal scintigraphy

Clinical signs / symptoms	Reflux nephropathy		
	Yes	No	Total
<i>With signs / symptoms:</i>	17*	1	18
▪ Hypertension (A)	10	-	
▪ Proteinuria (B)	14	1	
▪ Increased plasma ureum / creatinine (C)	10	-	
▪ A + B	2	-	
▪ A + C	1	-	
▪ B + C	3	-	
▪ A + B + C	5	-	
<i>Asymptomatic</i>	4	8	12
<b>Total</b>	<b>21</b>	<b>9</b>	<b>30</b>

\* One patient may suffer from one or more clinical signs / symptoms

Table 5. Correlation between the severity of reflux and renal scintigraphy

Severity of Reflux	Reflux nephropathy		
	+	-	Total
▪ Grade I - II	2	2	4
▪ Grade III - IV	5	2	7
▪ Grade V	3	0	3
▪ No reflux	4	4	8
▪ MCU not done	7	1	8
<b>Total</b>	<b>21</b>	<b>9</b>	<b>30</b>

Table 6. Other radiological findings

Findings	No
▪ Hydronephrosis	6
▪ Chronic pyelonephritis	5
▪ Neurogenic bladder	4
▪ Contracted kidney	2
▪ Hydroureter	2
▪ Obstructive uropathy	1
▪ Bladder diverticulum	1
▪ Urethral diverticulum	1

Hypertension was noted in 10 patients, proteinuria in 14, while the increment of blood urea and / or creatinine content was detected in 10 patients, 3 out of those patients were categorized as renal insufficiency and the remaining 7 patients as chronic renal failure. All of these 7 patients were derived from those patient who had bilateral renal scars. Of 22 patients examined completely with MCU and scintigraphy (Table 5) reflux of various grade were detected in 14 patients, 10 patients (71%) out of them showed renal scarring. The remaining 8 patients without reflux were composed of 4 with RN and 4 without RN. In the contrary, all but one case of the group without RN were asymptomatic.

Other radiological findings (detected by USG, IVP or other imaging examination) were shown in Table 6. Hydronephrosis with or without VUR was detected in 6 patients, chronic pyelonephritis in 5, and neurogenic bladder in 4 patients. Contracted kidney or small scarred kidney were found in 2 patients, and hydroureter in 2 patients. Obstructive uropathy, bladder diverticle, or urethral diverticle, each was found in one patient.

## Discussion

Urinary tract infection (UTI) is not rare in children. Obstructive uropathy and vesico-ureteral reflux (VUR) are the main predisposing factors especially in recurrent infection. Infected VUR can cause renal scarring or reflux nephropathy (NR). The higher the recurrence rate and the greater the grade of reflux, the greater the possibility of scar formation.<sup>6,7</sup> Once the disease protracted to RN, it will progress to renal failure and nothing could be done to stop this outcome. Thereby, effort should be directed toward early diagnosis and prompt treatment against UTI and the underlying anomaly before nephropathy appears. For this purpose, the role of the radiological investigation is very important.

The number of patients enrolled in this study cannot be considered as a real prevalence of UTI in our hospital since they come from selected patients as mentioned before. The prevalence of VUR in this study (64%) was higher than the prevalence rate reported in the literature. Previous study reported by Firman & Rahardjo in 1992<sup>8</sup> revealed that out of 35 patients with first attack of UTI, they only found 7 patients (20%) with vesicoureteral reflux. Peeden and Norman Noe<sup>9</sup> reported the prevalence rate of 38%, while Smellie and Normand<sup>10</sup> found the prevalence rate ranged between 20 to 50% of UTI patients in children. This discrepancy was not surprising because our study involved patients who had recurrent urinary infection for more than two times. The higher the frequency of infection, the higher the possibility of reflux will be identified. The prevalence rate of RN in our study (71%) was also higher compared with the reports of other authors. Olbing in 1987<sup>11</sup> predicted the prevalence rate of RN ranged between 10-24% of UTI patients. These findings could be explained by the fact that most of our patients were categorized as complicated UTI who suffered from infection several times, accompanied with various predisposing factors other than reflux.

The prevalence of RN in infected VUR in our study (71%) was also higher than the prevalence reported from literature. Goldraich and Barrat (1987)<sup>9</sup> for instance reported that the prevalence rate of scarred kidney in infected reflux ranged between 20-42%. Higher rate of recurrence of infection in our patients was probably responsible for this finding.

The duration of illness as seen in Table 3 revealed that almost 50% of patients suffered from recurrent infection less than 2 years. It is interesting to note here that the duration of illness was shorter in those patients with reflux nephropathy compared with those without nephropathy. This finding is unfortunately difficult to explain. Anyhow many reports stated that renal scarring can develop during six weeks after infection,<sup>11</sup> and new scars usually develop during the first five years of life when the kidney is more vulnerable to the combined effect of urinary tract infection and reflux."

Based on this phenomenon, the presence of renal scars during the period of less than two years in most patients could be apprehended. From the clinical data as shown in Table 4 we concluded that 17 out of 21 (63%) patients with renal scarring has reached the third phase of reflux nephropathy according to the natural history mentioned by Goldraich and Barrat.<sup>9</sup> It means that most of the patients diagnosed in a late state.

Proteinuria is the most important feature heralding a poor outcome in patient with reflux nephropathy. Once proteinuria has developed, the course of progression to renal failure is inexorable in a period of 5 to 10 years and maybe accelerated by malignant hypertension. Reflux nephropathy is an important cause of chronic renal failure in children and young adult. In a series of children with end-stage renal failure it was responsible for 9,6% up to 50% of patients reported by some authors.<sup>9</sup> Similar outcome was found in this study, 7 out of 21 patients of reflux nephropathy has progressed to renal failure, all of them originated from patients with bilateral renal scars.

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The gradation of reflux in this study did not correlate well with the presence of renal scarring (Table 4). Theoretically, the greater the grade of reflux the higher the prevalence of renal scarring;<sup>6</sup> but this is not always true; renal scar could even be present in the absence of reflux.<sup>10</sup> The gradation of reflux maybe diminished or spontaneously disappeared during the course of the disease while the scar formation still goes on.

The presence of various urological abnormalities found in this study as shown in Table 6 might be responsible for the formation of renal scars. Any urological abnormality that cause reflux or urinary stasis can promote scar formation in the kidney especially in those patients with recurrent urinary infection.

As a summary we concluded that the prevalence of VUR and RN in our patients with recurrent urinary tract infection were 63,6% and 70% respectively and the prevalence of RN in those patients with reflux was 71%. These figures are high in compare with the report in the literature. The high prevalence of RN in this study assumed not only due to VUR as a predisposing factor, but also due to other urological abnormality accompanied with UTI. st of patients come in a late state and some of them has progressed to renal failure. Once the disease has progressed to RN, further progression to renal failure is inevitable. The only effort could be done to prevent this disease is to detect the signs and symptoms of urinary tract infection and the related predisposing factors as early as possible. By early detection and prompt treatment including the administration of prophylactic antibiotics and surgical intervention when needed, scarring of the kidney can be prevented and at least further deterioration leading to renal failure can be avoided.

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