Prognostic Factors of Renal Scarring on Follow-up DMSA Scan in Children with Acute Pyelonephritis

Juyeon Lee, M.D.
Byung Woo Woo, M.D.
Hae Sook Kim, M.D.

Department of Pediatrics, Daegu Fatima Hospital, Daegu, Korea

*Announced on 23 October, 2015 fall conference of the Korean Pediatric Society
Corresponding author: Hae Sook Kim, M.D.
Department of Pediatrics, Daegu Fatima Hospital, 99, Ayang-ro, Dong-gu, 41199, Daegu, , Korea
Tel: +82-53-940-7243
Fax: +82-53-940-7076
E-mail: coreroro@hanmail.net

Received: 23 September 2016
Revised: 15 October 2016
Accepted: 19 October 2016

Purpose: Early diagnosis and treatment of urinary tract infection have been emphasized to prevent renal scarring. If untreated, acute pyelonephritis could cause renal injury, which leads to renal scarring, hypertension, proteinuria, and chronic renal failure. The purpose of this study was to assess risk factors of renal scarring after treatment of acute pyelonephritis (APN).

Methods: The medical records of 59 patients admitted at Daegu Fatima Hospital because of APN between March 2008 and April 2015 whose renal cortical defects were confirmed by using initial technetium-99m dimercaptosuccinic acid (DMSA) scans were reviewed retrospectively. We divided 59 patients into 2 groups according to the presence of renal scar and assessed risk factors of renal scar, including sex, age at diagnosis, feeding method, hydronephrosis, bacterial species, vesicoureteral reflux, and vesicoureteral reflux grade.

Results: Of 59 patients (41%), 24 showed renal scar on follow-up DMSA scan. No significant differences in sex, hydronephrosis, bacterial species, and fever duration were found between the renal-scarred and non-scarred groups. As for age at diagnosis, age of >12 months had 5.8 times higher incidence rate of renal scarring. Vesicoureteral reflux (VUR) affected renal scar formation. VUR grade III or IV had 14.7 times greater influence on renal scar formation than VUR grade I or II.

Conclusion: Our data suggest that the presence of VUR and its grade and age at diagnosis are risk factors of renal scar on follow-up DMSA scan after APN.

Key words: Acute pyelonephritis, Renal scar

Introduction

Five percent of febrile infants have a urinary tract infection. Most febrile patients with a urinary tract infection have acute pyelonephritis, and they can develop renal scarring. Patients with renal scars have a higher risk of hypertension and chronic renal failure. Early diagnosis and treatment of urinary tract infection in children under 2 years of age are necessary because of the higher incidence rate of renal scarring. Vesicoureteral reflux (VUR) affects renal scar formation. VUR grade III or IV has a greater influence on renal scar formation than VUR grade I or II.
of treatment, and recurrent urinary tract infections.

Technetium-99m dimercaptosuccinate (Tc-99m DMSA) is the most sensitive diagnostic tool to identify acute pyelonephritis during the acute phase of a febrile urinary tract infection and furthermore pinpoint the area that will subsequently develop into a renal scar 3 to 6 months after the infection. About 42-60% of patients with acute pyelonephritis develop renal scars. Therefore, we evaluated studies in which acute pyelonephritis was diagnosed and followed up with DMSA scans. The aim of this retrospective clinical study was to determine the incidence of renal scarring after acute pyelonephritis, duration of fever, level of C-reactive protein (CRP), species of bacteria, and VUR and its grade.

Materials and methods

The medical records of 59 patients whose renal cortical defects were confirmed by DMSA scan when admitted to Daegu Fatima Hospital for their first febrile urinary tract infection from March 2008 to April 2015 were reviewed retrospectively. A follow-up DMSA scan was performed within 6 months after the last urinary tract infection with renal cortical defects. The DMSA scan was considered abnormal if one or more areas of decreased cortical uptake were noted with or without preservation of the cortical outline. Other urogenital tract anomalies were excluded.

We divided our clinical series of patients into the following 2 groups: the renal-scarred group and the non-renal-scarred group on the follow-up DMSA scan. Data on the following items were analyzed: age at diagnosis, sex, duration of fever before treatment, total duration of fever, white blood cell count, CRP level, erythrocyte sedimentation rate (ESR), hydronephrosis, feeding method, and voiding cystourethrogram (VCUG) results.

Febrile urinary tract infection was defined as fever ≥38°C, pyuria, or growth of at least 100,000 colony-forming units per milliliter of a single bacterial species from midstream or catheter specimens. Hydronephrosis was defined as ≥5 mm of renal pelvic anteroposterior (AP) diameter on sonograms. VCUG was used for detection and grading of VUR. VUR was graded as follows: Grade I reflux was defined as reflux limited to the ureter; grade II was reflux up to the renal pelvis; grade III was reflux into a mildly dilated ureter and pelvicaliceal system; grade IV was a moderately dilated ureter and blunting of the fornix; and grade V was a tortuous ureter with severe dilation of the ureter and pelvicaliceal system. Laboratory data that are markers of inflammation, including CRP and ESR, during acute pyelonephritis were collected. As for age at diagnosis, we divided our clinical series of patients into two groups: <12 months and ≥12 months. To investigate the protective effect of breastfeeding against urinary tract infection, we grouped the patients into 3 groups by feeding method: breast-fed, formula-fed, and breast- and formula-fed.

Results

Of the 59 patients who had cortical defects on initial febrile urinary tract infection, renal scarring was found on follow-up DMSA scan in 24 (41%) patients. Table 1 shows the clinical characteristics and laboratory findings of all patients.

1. Renal Scarring and Age at Diagnosis

The 24 patients who had renal scarring on follow-up DMSA scan included 10 (42%) boys and 14 (58%) girls.
There was no significant difference between boys and girls in terms of developing renal scars ($P=0.93$).

The mean age at diagnosis was 15.2 months. Patients with scars on follow-up DMSA scan were significantly older (mean age: 23±24.5 months) than those who did not have scars (mean age: 10±15.7 months).

We also divided patients into two groups according to age: under 12 months old and over 12 months old. Children over 12 months old were 5.83 times more likely to develop renal scars than those under 12 months ($P=0.01$, Table 2).

### 2. Feeding Method

As ongoing exclusive breastfeeding and an extended duration of breastfeeding are associated with a significantly lower risk of infection\(^8\), we grouped patients by feeding method into the breast-fed group, formula-fed group, and breast- and formula-fed group. There was no statistically significant difference in feeding method ($P=0.69$, Table 3).

### 3. Hydronephrosis

We investigated correlations between hydronephrosis and renal scars. Twenty-one (36%) of 59 patients had hydronephrosis on ultrasound. There was no statistically significant difference between patients with hydronephrosis and renal scars ($P=0.80$, Table 4).

### 4. Distribution of Causative Organisms

A total of 48 patients (81%) out of 59 had positive urine cultures. There was no growth on urine culture in 11 out of 59 patients (Fig. 1). The most common pathogen was *Escherichia coli* (*E. coli*). We found no correlations between the pathogens and the incidence of renal scars ($P=0.72$).

### 5. CRP, ESR, and WBC

We found no difference between the groups with or without scars in regard to the level of CRP, ESR, or WBC count at the time of infection (Table 1).

### 6. VUR and VUR Grade

VUR was found in 23 (39%) patients after their first febrile urinary infection. There was a correlation between VUR and renal scarring on DMSA scan within 6 months after the first febrile urinary tract infection ($P=0.00$). Renal scarring was significantly more common in patients with grade ≥3 reflux than in patients without reflux. VUR I–II groups had a 1.57 times greater incidence rate of scarring than the group with no reflux. Furthermore, VUR III–IV groups had a 14.7 times greater incidence rate of scarring than a comparable group with no reflux (Table 5).

---

**Table 2. The Difference of Renal Scars according to Age at Diagnosis**

<table>
<thead>
<tr>
<th>Age</th>
<th>No. (%) of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No scar</td>
<td>Scar</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>30 (70)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>≥12 months</td>
<td>5 (31)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (59)</td>
<td>24 (41)</td>
</tr>
</tbody>
</table>

*$P=0.01$. *Odds ratio=5.83.

**Table 3. The Difference of Renal Scars according to Feeding Method**

<table>
<thead>
<tr>
<th>Feeding method</th>
<th>No. (%) of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No scar</td>
<td>Scar</td>
</tr>
<tr>
<td>Breastmilk</td>
<td>17 (55)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Formula</td>
<td>11 (61)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Mixed</td>
<td>7 (70)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (59)</td>
<td>24 (41)</td>
</tr>
</tbody>
</table>

*$P=0.69$.

**Table 4. The Difference of Renal Scars according to Hydronephrosis**

<table>
<thead>
<tr>
<th>Hydronephrosis (diameter≥5 mm)</th>
<th>No. (%) of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No scar</td>
<td>Scar</td>
</tr>
<tr>
<td>Negative</td>
<td>23 (61)</td>
<td>15 (40)</td>
</tr>
<tr>
<td>Positive</td>
<td>12 (57)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (59)</td>
<td>24 (41)</td>
</tr>
</tbody>
</table>

*$P=0.80$.

**Fig. 1. The difference of renal scars according to causative organisms.**
Table 5. The Difference of Renal Scars according to the Grade of VUR

<table>
<thead>
<tr>
<th>VUR</th>
<th>No. (%) of patients</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No scar</td>
<td>Scar</td>
</tr>
<tr>
<td>No reflux</td>
<td>27 (75)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>I-II</td>
<td>5 (71)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>III-IV</td>
<td>3 (19)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (59)</td>
<td>24 (41)</td>
</tr>
</tbody>
</table>

*p=0.00.

Discussion

It has been suggested that some defects seen on scans carried out within three months of a urinary tract infection may be transient\textsuperscript{10}. It is uncertain how much scarring is sustained at the time of the first urinary tract infection. As for age at diagnosis, there have been many conflicts between studies. Gleeson and Gorden suggested that children under 1 year of age have a higher possibility of renal scarring\textsuperscript{10}, whereas Jakosson and Svensson reported that children over 1 year of age have a much greater possibility of developing renal scars after initial infection\textsuperscript{11}. The growing kidney could be more susceptible to inflammation and incompetence, and VUR is more likely to be present\textsuperscript{12}. However, in our study, we found that children with scars were older at the time of acute pyelonephritis than those without scars. It is possible that some older children with pyelonephritis may have had an undetected urinary tract infection during infancy. This would mean that a delay in diagnosis and treatment of urinary tract infections can be a factor in the development of scarring.

Many studies demonstrated that breastfeeding seems to protect against several forms of infection. Mårild et al. noted a protective effect of breastfeeding against urinary tract infections\textsuperscript{12}. Usually it can be understood that the main protective factors of human milk function by preventing infectious agents from attacking the host via the mucosal membranes\textsuperscript{12}. Lactoferrin, which is a major milk protein, not only efficiently kills various microbes, but does so without inducing inflammation. This is why we studied the correlations between breastfeeding and renal scars after acute pyelonephritis. However, no obvious correlation between breastfeeding and good protection was seen. In our group, 53% of the patients were only breastfed, and 17% were breast- and formula-fed. We considered only the breast-fed group when considering the protective effects of human milk, but the results showed no positive effect of breastfeeding.

The correlation of hydronephrosis and urinary tract infection has been much discussed so far. One study showed that the most common cause of collecting system dilatation was VUR\textsuperscript{13}. Although ultrasonography could not precisely detect VUR, hydronephrosis accompanied by acute pyelonephritis could be considered. We investigated whether hydronephrosis could have an effect on the development of renal scars. However, in our study, having hydronephrosis at time of initial urinary tract infection did not have any impact on the development of renal scars.

We found no difference between the groups with or without scars in regard to the duration of fever or the CRP or WBC levels at the time of infection. Delay in treatment has a close relationship with an increased frequency of renal scarring. Most of the children were referred to our hospital in 3–4 days of fever; therefore, our study suggests that there is no difference between the level of inflammation and the formation of renal scars, whereas some studies report that there is a correlation between the level of CRP and renal scarring\textsuperscript{14}.

It has been emphasized that pyelonephritis in children is commonly associated with P-fimbriate E. coli, both in the presence and absence of VUR\textsuperscript{15}. In our study, we did not study the bacteria with regard to P-fimbriae, but there was no correlation between pathogens and renal scars.

VUR is the retrograde passage of urine from the bladder into the ureter. According to the intrarenal reflux nephropathy theory, patients who have VUR can easily develop permanent renal scarring after their first febrile urinary tract infection\textsuperscript{16}. The International Reflux Study Committee grades VUR from grade I to V\textsuperscript{17}. Grading is important because of the prognosis. The incidence of intrarenal reflux starts to decrease from 6 years old, and as the kidney grows it rarely leads to renal scars\textsuperscript{18}. Thus, VUR has been considered to be a possible risk factor for the development of renal scars. The role of VUR as a prerequisite may be related as a risk factor for acute pyelonephritis. Although 61% of the scarred kidneys in our study had no VUR, our study showed that having VUR increases the risk of renal scars.

In our study, the incidence of renal scarring became higher with increased VUR grades. VUR III-IV groups had a 14.7
times greater incidence rate than in a comparable group with no reflux.

In our study, renal scarring was associated with VUR with its grade and urinary tract infection with its grade. Additionally, a delay in diagnosis and treatment of urinary tract infection could lead to renal scarring, as children diagnosed at an older age had a higher possibility of renal scars. We recommend that many children could benefit from further investigation that might prevent the development of the scarring process and renal complications.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References


15. Majd M, Rushton HG, Jantausch B, Wiedermann BL. Relationship among vesicoureteral reflux, Pfimbriated E. coli, and acute pyelo-