Abstract

Objective: to determine the incidence of renal scars in children with primary vesicoureteral reflux taking into consideration the following variables: sex, age at diagnosis, febrile urinary infection, degree of reflux and bacteria specimen.

Method: retrospective study of 58 children with age ranging from 2 months to 11 years, presenting primary vesicoureteral reflux detected by voiding cystourethrogram after documented episode of urinary tract infection. The diagnosis of renal scarring was obtained by dimercaptosuccinic acid scan 5 months after the treatment of the urinary infection; in 40 children the dimercaptosuccinic acid scan was performed again from 6 months up to 6 years after the treatment.

Results: 45 children (77.6%) were girls and 13 (22.4%) were boys, 51.7% were 2 years old or younger. The incidence of renal scarring was 55.2%. There was significant higher proportion of renal scars in girls, when the patients presented fever and dilated vesicoureteral reflux (III, IV, V). Fever and female sex were risk factors for the development of renal scars (fever - ODDS ratio = 6.19 and female sex - ODDS ratio = 4.12). There was a prevalence of renal scars in children over 2 years old. The interval between the beginning of the symptoms and the first medical visit was longer in the children with renal scars. New renal scars were observed in 12.5%.

Conclusions: fever and female sex were risk factors for the presence of renal scars, mainly in the dilated vesicoureteral reflux. The high incidence of renal scars in this study may be related to delayed diagnosis of vesicoureteral reflux.

Introduction

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder back up the ureter(s) and in humans is an abnormal event. The frequency of VUR in children varies inversely with age. Between 0.5% and 1% of asymptomatic children have VUR and it is estimated that 35% of all children with symptomatic urinary infections will have VUR. Urinary infection is the most common factor leading to the discovery of VUR.

In 1975 urinary infections presented by patients with vesicoureteral reflux were described as being associated with the formation of renal parenchyma lesions, and it was accepted that VUR was pre-requisite to the formation of further renal lesions.

During the last nineties it was recognized that other factors such as bacterial virulence, vesical dysfunction and genetic susceptibility in addition to VUR, cause or contribute to the development of renal lesions.

The appearance of a renal lesion may result in sequelae for patients; between 6 and 13% of children with renal scarring will develop arterial hypertension and in 5 to 10% are the cause of chronic renal failure.

The identification of children with VUR at early ages offers the opportunity to prevent episodes of acute pyelonephritis and the possible formation of renal scars. Once renal scarring has been diagnosed, continuous observation of the child becomes necessary because of the problems which result from such lesions and the study of factors associated with the formation of renal scars can be useful in evaluating such patients.

The objective of this study was to ascertain the incidence of renal scarring among patients with primary vesicoureteral reflux, comparing sex, age at diagnosis, infectious fever, degree of reflux and type of bacteria.

Methods

Patients

This is a retrospective study of cases selected from among 159 children with urinary infection registered and under observation at the Pediatric Nephrology Clinic of the Pediatric Department of the Botucatu Medical Faculty - UNESP, a secondary and tertiary referral Pediatric service, during the period between January 1992 and December 2001. Within this period 69/159 (43.4%) of the patients presented VUR, of these 60 presented primary VUR, although only 58 patients underwent renal scintigraphy with DMSA at the beginning of observation and it is these who constitute the population studied. Children of both sexes were studied, aged between 2 months and 11 years (mean of 3.1 ± 2.8 years), suffering from urinary infections and primary vesicoureteral reflux (VUR).

Children were excluded if they had been under observation for less than 6 months or if they had pathologies associated with the presence of secondary VUR such as posterior urethral valves or neurogenic bladder or Prune Belly syndrome or dysfunctional voiding. Those with dysfunctional voiding were identified by a clinical history positive for symptoms such as: nocturnal and/or diurnal incontinence, urgency incontinence and elevated voiding frequency associated with recurrent urinary infections, intestinal constipation, soiling which usually have their onset during toilet training; and by abnormalities detected with ultrasound such as; vesical thickness greater than 3 mm with a full bladder, vesical capacity above two standard deviations from the norm for their age and post-voiding residue greater than 5% of the total vesical volume.

The diagnosis of urinary infection was made by urine culture which was collected by vesical catheter from children less than 2 years old and in mid-stream for older children. Urine samples can be taken with a collection bag (U-bag) or, preferably, mid-stream as long as they are performed by means of appropriate techniques.

The work was approved by the Committee for Ethics in Research of the Hospital das Clínicas of the Botucatu Medical Faculty -UNESP.

Clinical parameters: sex, age at onset of symptoms, age at start of observation at the unit, height and weight, urinary infection symptoms presented at the diagnosis. Fever was one of the most frequent symptoms; the occurrence of fever was ascertained by means of a questionnaire asking about body temperature measurement which was completed at the unit, when the child was seen in Emergency, or in another consulting location.

Imaging studies: for all children, VUR investigation was performed after the diagnosis of urinary infection. Diagnosis of VUR was made by voiding cystourethrography (VCR). At the unit, VCR is performed on children with urinary infections from zero to 5 years of age of both sexes, on boys of all ages and on girls over five years of age who have repetitive infections or with dilatation diagnosed by renal ultrasound or with suspicion of vesical instability. The degree of VUR was classified from I to V according to International VUR classifications. Voiding cystourethrography was performed a minimum of four weeks after treatment for urinary infection. Vesicoureteral reflux with dilatation was diagnosed for renal units with third to fifth degree VUR and undilated in cases of first and second degree VUR. In cases where the patient had bilateral VUR, the VUR was diagnosed as being of a higher degree.

The presence of renal scarring was assessed by renal scintigraphy with DMSA performed at a minimum of five months after treatment for urinary infection. The test was repeated in the cases of 40 children and results were taken from the first and last tests. The test was performed at the Nuclear medicine Unit of the Botucatu Medical Faculty-
UNESP by the member of that service with previous experience of urinary infection diagnosis but not always with knowledge of the patient’s VUR diagnosis. Renal scarring was diagnosed if areas of reduced capture were present in the renal parenchyma. Renal scarring was evaluated for patients, and for individual kidneys only presence or absence of renal scarring was considered.

**Treatment:** Thirty-seven children (60%) were prescribed antibiotics (cephalexin or amikacin or gentamycin or cefuroxime or ceftriaxone), primarily those less than 2 years old (20/31-64.5%). After this initial treatment, prophylactic treatment was begun with cephalixin or nalidixic acid or nitrofurantoin for all of the children. Corrective surgery was performed on two of the 26 ureters with third degree VUR, on nine of the 10 with fourth degree VUR and on two fifth degree ureters.

**Statistical analysis**

Results were expressed as mean standard deviation, median or percentage.

For the analysis of data computer software entitled SAS for PC, version 6.12 (SAS Institute, Cary, NC) was employed. The Chi-square test or Fisher’s exact test were used, when relevant; for the evaluation of male/female ratios, age group ≤ or > 2 years at the start of observation, presence or not of fever, etiologic agent (*E. coli* or other), Dilated VUR or undilated and left or right for those patients with VUR and renal scarring.

The Mann-Whitney non-parametric test was used for comparisons between medians for the presence or absence of renal scarring with the interval between the appearance of symptoms and consultation at the clinic, and with the age of the patient at the onset of symptoms.

Data which upon univariate analysis returned p < 0.25 values were then subjected to multivariate analysis, using the logistic regression model, with the aim of simultaneously evaluating the influence of each variable on the incidence of renal scarring. Statistical significance was defined as p ≤ 0.05.

**Results**

Table 1 contains the clinical patient characteristics age, sex, side and degree of VUR.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male 13</th>
<th>Female 45</th>
<th>Total (%) 58 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset of symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 1 year</td>
<td>9</td>
<td>30</td>
<td>39 (67.2)</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>4</td>
<td>15</td>
<td>19 (32.8)</td>
</tr>
<tr>
<td><strong>Age at VUR diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 1 year</td>
<td>6</td>
<td>6</td>
<td>12 (20.7)</td>
</tr>
<tr>
<td>1 to 2 years</td>
<td>5</td>
<td>13</td>
<td>18 (31.0)</td>
</tr>
<tr>
<td>2 to 4 years</td>
<td>0</td>
<td>8</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>&gt; 4 years</td>
<td>2</td>
<td>18</td>
<td>20 (34.5)</td>
</tr>
<tr>
<td><strong>VUR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated (I to II)</td>
<td>4</td>
<td>10</td>
<td>17 (24.2)</td>
</tr>
<tr>
<td>Dilated (III to V)</td>
<td>4</td>
<td>14</td>
<td>18 (31.0)</td>
</tr>
<tr>
<td><strong>Bilateral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated / undilated</td>
<td>1</td>
<td>7</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Undilated / dilated</td>
<td>2</td>
<td>7</td>
<td>9 (15.5)</td>
</tr>
<tr>
<td>Dilated / dilated</td>
<td>2</td>
<td>7</td>
<td>9 (15.5)</td>
</tr>
</tbody>
</table>
children presented weight below the fifth percentile and seven stature below the fifth percentile. All presented arterial pressure within normal limits.

Fever was observed in 84.5% of the patients and as the only symptom in 39.6% of cases (23/58). Other isolated symptoms or symptoms associated with fever were macroscopic hematuria in 17.2%, abdominal pain in 13.8%, failure to gain weight in 10.3% and dysuria in 10.3%. In 48 children (82.8%) urinary infection symptoms had their onset before they were two years old.

The most common etiologic agent was *E coli*, in 46 children (79.4%), followed by *Proteus* in five (8.6%), *Enterobacter* in four (6.9%), *Klebsiella* in two (3.4%) and *Enterococcus faecalis* in one (1.7%).

Unilateral vesicoureteral reflux was observed in 32 children (55.2%) and bilateral in 26 (44.8%). In 36 children (62.1%) dilated VUR was observed and, of these, nine presented fourth degree VUR and two fifth degree. The total number of renal units with VUR was 84. Of these, first degree VUR was observed in 18 (21.4%), degree II in 21 (25.0%), degree III in 33 (39.3%), degree IV in 10 (11.9%) and degree V in two (2.4%).

Table 2 illustrates the number of patients with renal scarring in relation to sex and to degree and side of VUR.

The initial DMSA revealed 32 children (55.2%) presenting renal scarring. Two female children, one, an eleven year-old with second degree VUR on the left and the other, who was six years and six months old, with bilateral VUR, first degree on the right and fourth degree on the left, presented renal failure on the sides with second degree and fourth degree VUR, respectively. In response to the difficulty in differentiating between renal failure as a result of the scarring or as a result of congenital lesions, the scarring of these kidneys was not considered to be the cause of the failure.

Table 3 contains the statistical analysis of the comparison of the parameters sex, age group at start of observation, fever, etiologic agent and degree and side of VUR between patients with or without renal scarring.

Among the patients with renal scarring, a significantly greater proportion of female children was observed and also a tendency towards children more than two years old.

The median of age at onset of symptoms was significantly greater among children with renal scarring (median = 1 year, P25 = 0.6 and P75 = 1.9 as against median = 0.6 year, P25 = 0.25 and P75 = 1.0, p = 0.04). The median of the interval between the onset of symptoms and the first consultation was also significantly greater.

### Table 2 - Number of patients with renal scarring according to sex, degree and side of vesicoureteral reflux (VUR)

<table>
<thead>
<tr>
<th></th>
<th>Male (13)</th>
<th>Female (45)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with renal scarring</td>
<td>4</td>
<td>28</td>
<td>32 (55.2)</td>
</tr>
<tr>
<td>Unilateral VUR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undilated (I to II)</td>
<td>0</td>
<td>4</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Dilated (III to V)</td>
<td>4</td>
<td>9</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Bilateral VUR *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ undilated / + undilated</td>
<td>0</td>
<td>2</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>– undilated / + undilated</td>
<td>0</td>
<td>2</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>+ undilated / + dilated</td>
<td>0</td>
<td>1</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>+ undilated / – dilated</td>
<td>0</td>
<td>1</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>– undilated / + dilated</td>
<td>0</td>
<td>4</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>– dilated / + dilated</td>
<td>0</td>
<td>2</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>+ dilated / + dilated</td>
<td>0</td>
<td>3</td>
<td>3 (9.3)</td>
</tr>
</tbody>
</table>

* in patients with bilateral VUR the symbol – indicates absence of renal scarring and the symbol + indicates presence of renal scarring.
for the children with renal scarring (median = 1.3 years, P25 = 0.5 and P75 = 3.0 compared with median = 0.6 years, P25 = 0.3, P75 = 1.3, p = 0.04).

There was a significantly greater proportion of children who had presented fever among those with dilated VUR: 33 presented fever compared with 16 who had undilated VUR, p = 0.05.

There was no statistical difference between cases of identification of E. coli or other bacteria among children with renal scarring.

Considering the 84 renal units with VUR, renal scarring were observed in: 6/18 (33.3%) with first degree VUR, 6/22 (27.3%) at degree II, 16/35 (45.7%) at degree III and 7/10 (70.0%) at degree IV and 1/2 (50%) at degree V. Renal scarring was observed in a significantly greater proportion of units with dilated VUR compared with those with undilated VUR. No statistically significant difference was observed between unilateral and bilateral VUR.

The results of the multivariate analysis revealed that risk factors significant to the incidence of renal scarring were female sex and the presence of fever. The calculation of the risk of occurrence of renal scarring, in the form of chance or odds ratio, demonstrated that female children present a risk 4.12 times greater than male children (95% confidence interval = 1.046 - 16.215, p = 0.04); and children of both sexes with fever present a 6.19 times greater risk than those without fever (95% confidence interval = 1.111 - 34.512, p = 0.03).

An assessment of the evolution of renal scarring by DMSA was performed for 40 children, 21 with bilateral VUR. The period between the first and last assessment examination was similar among patients with no scarring at the initial DMSA (1 to 3 years, mean of 2.1 ± 0.7 years) and those with renal scarring (6 months to 6 years, mean of 2.7 ± 1.8 years).

Of the 16 children with no renal scarring at the initial DMSA, four (25%) developed renal scars during an average period of 2.4 ± 0.5 years. Of these, two females aged 7 and 11 months, presented third degree unilateral VUR and presented repetitive infections during observation. One 1 year and 4 month old female child with second degree unilateral VUR did not present repetitive infection, but developed scarring during the 2 year and 3 month observation period. One 5 year and 5 month old boy with fifth and first degree VUR did not present renal scarring at the initial DMSA, but during the 1 year observation period developed scarring of the renal unit with fifth degree VUR and did not have repetitive infection.

From 24 children with renal scarring at the initial DMSA, one (4.2%) suffered an increase in renal scarring during the 1 year and 4 month observation period, had bilateral, third degree VUR with scars on only one kidney at the initial DMSA and presented repetitive infection. Twenty-three of these patients (95.8%), presented unchanged renal scars when compared with the initial examination. Out of a total of 40 patients with VUR, 5 (12.5%) developed new renal scars.

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n of children with renal scarring</th>
<th>n of children without renal scarring</th>
<th>Total</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female</td>
<td>4/28</td>
<td>9/17</td>
<td>13/45</td>
<td>0.4</td>
</tr>
<tr>
<td>Age group ≤ 2 years / &gt; 2 years</td>
<td>12/20</td>
<td>18/8</td>
<td>30/28</td>
<td>0.06</td>
</tr>
<tr>
<td>Fever / no fever</td>
<td>30/2</td>
<td>19/7</td>
<td>49/9</td>
<td>0.03</td>
</tr>
<tr>
<td>Etiologic agent E. coli / other</td>
<td>27/5</td>
<td>19/7</td>
<td>46/12</td>
<td>0.14</td>
</tr>
<tr>
<td>Dilated VUR / undilated</td>
<td>23/9</td>
<td>13/13</td>
<td>36/22</td>
<td>0.04</td>
</tr>
<tr>
<td>Unilateral VUR / bilateral VUR</td>
<td>17/15</td>
<td>15/11</td>
<td>32/26</td>
<td>0.77</td>
</tr>
</tbody>
</table>

* significant p ≤ 0.05.
Discussion

In this study, the percentage of patients with renal scars was similar to that described in the scientific literature, where incidences vary between 30 and 70%.15-19 The variability of this incidence may, in part, be influenced by the method of diagnosing renal scarring. Studies which diagnosed renal scarring by means of intravenous pyelography found incidences between 34 and 49%.14,16,20 Studies of VUR sufferers which made their assessments by DMSA over periods of between 3 months and 2 years after the acute urinary infection phase detected the presence of scars in between 36 and 52% of kidneys.7,21 Renal scintigraphy with DMSA is considered to be the most sensitive test for the diagnosis of renal scarring22,23 and it is possible that this is the differentiating factor in the greater incidence (55.2%) observed in this study.

The area of a renal lesion is quantified by scintigraphy with DMSA to be used in differentiating between congenital and acquired renal scarring.24 A global reduction in radionucleotide capture indicates a congenital alteration while focal capture defects indicate acquired scars.24 The two children who had renal failure shown up by DMSA may be considered to be suffering from congenital alterations. Focal radionucleotide capture defects are reported with older children.25 The data produced by our work suggests that our patients with renal scarring presented the acquired form since we observed a greater proportion of these lesions among older children.

Among predominantly male children who had been found to have had severe vesicoureteral reflux (third to fifth degree) with prenatal ultrasound examinations, the incidence of renal scars obtained by DMSA was from 17 to 60%.7,25 In the absence of previous urinary infection, these lesions are explained by phenomena which occurred during renal development resulting in renal dysplasia and/or hypoplasia.7 In this study, three out of four boys with Vesicoureteral reflux with dilation and renal scarring were less than 1 year old, and, despite the diagnosis of VUR and of renal scarring having been made after urinary infections, it is possible that a proportion of these scars are of this origin.

A little described factor is the influence that sex has on children with VUR and renal scarring. In contrast with the observations we have made, there are reports in which a greater proportion of renal scar patients are boys25 or in which sex has no influence on the incidence of renal scarring.9 Nevertheless, in the present study, the female sex was at significantly greater risk of renal scarring. This fact may be due to the greater susceptibility to urinary infection of girls older than six months, since the relatively short length of the ureter makes it easier for bacteria to gain access to the bladder.5 Vesicoureteral reflux combined with the capacity which E coli has to adhere to the uroepithelial cells also facilitate the bacteria’s ascent to the bladder.5 Associated with the factors already mentioned, it is known that there is a higher rate of recurrent urinary infection among girls.5 Thus, constant observation is recommended of children, particularly females, who have febrile urinary infections and VUR with or without renal scarring.

When children with urinary infections have been assessed using intravenous pyelography, younger age groups have been related with higher risks of renal scarring.26 However, using DMSA a higher frequency of permanent lesions were found among children more than two years old.27

When children with VUR were assessed with intravenous pyelography or DMSA, renal scarring had a greater incidence among those less than two years old.20,21 In this study, the incidence of renal scars was greater among children over two. This fact could be associated with the higher proportion of children over two with a probable late diagnosis of urinary infection included in the study.

In the presence of vesicoureteral reflux, 80 to 90% of patients with febrile urinary infections present alterations to DMSA results compatible with acute pyelonephritis.7,24 In this study, those children who presented fever, probably also presented pyelonephritis the resolution of which was renal scars detected by DMSA, since fever was a risk factor for renal scarring and VUR. Furthermore there were delays between the onset of symptoms and the first consultation. Studies report a correlation between the severity of renal scars and the lateness of diagnosis with children with VUR.28

P fimbria has been identified as an agent of E coli bacterial virulence which is both a factor in adherence and a contributor to the formation of renal scars.29 In children with pyelonephritis a similar level of E coli was observed among both those who developed renal scarring and those who did not,30 in common with this study. This raises questions about the greater risk of scar formation in patients infected by P-fimbriated E coli.7,25,30

Nowadays certain authors question the role of vesicoureteral reflux in the development of renal scars, since in some studies of observation post-pyelonephritis patients a greater proportion of renal scarring was found among those who did not have vesicoureteral reflux.24 While there is evidence that infection of the renal parenchyma and not VUR is the pre-requisite for the formation of renal scars,24 they are still more common in kidneys which have had VUR of the third degree or greater when compared with kidneys which have had no VUR or low-degree VUR;17,21,24 which findings are similar to ours.

A study of 5 years’ observation for the evaluation of renal scarring by DMSA reported an incidence of 17% of alterations, predominantly observed among children...
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under two years old, with bilateral, fourth degree VUR, the incidence of new scarring was similar to that observed in this study.

In this study fever and female sex were factors of greater risk for the presence of renal scars, particularly with Vesicoureteral reflux with dilation. The elevated incidence of renal scarring could be related to the delayed VUR diagnosis and the lower incidence of renal scarring to the use of prophylactic antibiotics and control of the urinary infection.

In the light of the results of this study, and of the vast amount of literature on primary VUR with contrasting reports of the varied aspects approached, what stands out is the importance of early VUR diagnosis in children with febrile urinary infections and the effective employment of prophylaxis with antibiotics or chemotherapy to control infection. In order to clear up points of doubt in relation to the “nephropathy of reflux” it is important that studies of large samples of patients be performed, employing multivariate statistical analysis models.

References


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