CLINICAL PROFILES AND OUTCOMES OF RENAL SCARRING IN CHILDREN UNDERWENT DIMERCAPTOSUCCINIC ACID (DMSA) RENAL SCAN IN A TERTIARY HOSPITAL

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Introduction: Renal scarring, which can be detected by DMSA renal scan, has been demonstrated to cause hypertension, proteinuria and chronic kidney disease (CKD). We reviewed the proportion of renal scarring, risk factors and outcomes among children who were referred for DMSA scan in a tertiary teaching hospital. Methods: All records of children less than 18 years old who underwent DMSA scan over a ten-year period, were reviewed. Among children whose renal cortical defects were confirmed by DMSA scan, data of their risk factors and its outcome were collected manually. Results: Out of 92 children referred for DMSA scan, half were detected to have renal scarring. Vesico-ureteric reflux (VUR) was significantly associated with the development of renal scarring. CKD (27.1%) and hypertension (12.5%) were the commonest complications. The median duration between diagnosis of the complications and detection of renal scarring was 1 year. Conclusion: A high proportion of children undergoing DMSA scans had renal scarring and early development of serious complications was common.

Keywords: Renal Scarring, Vesico-ureteric Reflux, Dimercaptosuccinic Acid Renal Scan, Chronic Kidney Disease

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Introduction
Pyelonephritis in children under 5 years of age leads quite often to renal scarring, which is an established risk factor for hypertension, proteinuria and chronic kidney disease (CKD) [1,2]. The prevalence of renal scarring in urinary tract infections and children with urinary reflux were 31% and 47% respectively [3]. Urinary tract infection (UTI) occurs more common in boys than girls in the first year of life and 10 times higher in uncircumcised boys. The incidence of UTI falls below 1% in school-aged boys and increases to 1-3% in school-aged girls [4,5]. Factors that may predispose to renal scarring include congenital anomalies of kidney and urinary tract (CAKUT), comprising of VUR, horseshoe kidney, duplex kidney, or any obstruction of the urinary system [6]. Dimercaptosuccinic acid (DMSA) renal scan is a nuclear medicine scan that uses the radiopharmaceutical Tc-99mDMSA and involves radiation exposure to the children. DMSA renal scan has been universally used to detect renal scarring and it helps to determine the relative function of kidneys [7,8]. Hypertension has been demonstrated in children as early as 8 years after detection of renal scarring [9]. Nevertheless, there are limited studies on looking at the time taken to develop other complications of renal scarring like CKD and proteinuria. This study aimed to determine the proportion of renal scarring among children undergoing DMSA scans in a tertiary hospital and to describe risk factors and outcomes in this study population.

Materials and Methods
This was a cross-sectional study conducted in Hospital Universiti Sains Malaysia (USM), Kubang...
Kerian, is a tertiary centre located on the east coast of Peninsular Malaysia. All records of children less than 18 years old who were referred for DMSA renal scan beginning from the 1st January 2008 until 31st December 2019 were reviewed. Records with inadequate data or outcomes occurred at the end of the study period was excluded. The medical records retrieved were reviewed retrospectively using a data collection sheet containing patient's information and determinants. Data on their risk factors which include recurrent urinary tract infections (UTI), CAKUT and VUR were obtained while data on the renal scarring outcomes which include proteinuria, hypertension and CKD were obtained from children with abnormal DMSA scans.

The results of the DMSA scans were reported by Nuclear Medicine Physician based on the presence or absence of renal scarring and estimation of relative renal function of kidneys. Based on the International Reflux Research Committee classification system, low-grade VUR is classified as VUR grade III and below, whereas high-grade VUR is defined as VUR grades IV onwards [10].

Hypertension is defined as blood pressure in the 95th percentile or higher for age, height and sex [11]. CKD is defined based on KDIGO 2012, abnormalities of kidney structure or function and based on GFR categories which present for more than 3 months [12].

This study received ethical approval from Human Research Ethics Committee Universiti Sains Malaysia (USM/JEPeM/19010090) and Medical Research and Ethics Committee Kementerian Kesihatan Malaysia (NMRR-19-3454-45925).

**Statistical analyses**

Numerical data were presented as mean ± standard deviation (SD) and median ± interquartile range (IQR), depending on the distribution of the data. Categorical variables were expressed as frequencies and percentages. Comparison of categorical data was performed either using Pearson Chi-Square test or Fisher’s exact test to determine the association between risk factors and the development of renal scarring, and association between risk factors and outcomes of renal scarring. A probability value ($P$-value) of less than 0.05 was considered to be statistically significant.

**Results**

The initial cohort consisted of 127 children who were referred to the nuclear medicine department for a DMSA scan. Ninety-two cases were eligible to be analysed after 35 were excluded due to incomplete data ($n=20$) or age more than 18 years old at the time of imaging ($n=15$). The study population consisted of comparable numbers of male and female children with the majority were Malays (93.5%). The median age was 5.0 years. The main indication for DMSA scan was VUR ($n=59$, 64%) while the remaining reasons for referral were to assess kidney function among children with CAKUT. Nine of them (9.8%) had duplex kidney, 3 (3.3%) posterior urethral valves, 5 (5.4%) pelvi-ureteric junction (PUJ) or vesico-ureteric junction (VUJ) obstruction and 3 (3.3%) multicystic dysplastic kidney. Among children undergoing DMSA scan, half had renal scarring.

Table 1 describes the association between risk factors and renal scar formation in children. There was a significant association between VUR and DMSA abnormalities. Forty-two out of forty-eight children with renal scarring had underlying VUR. Fourteen (33.3%) of them had low grade and twenty-eight (66.7%) had high-grade VUR. More than half of children with VUR ($n=36$) presented with recurrent UTIs while another 23 children had no documented history of recurrent UTI.

Non-E.coli organisms (75.0%) seemed to be the main cause of renal scarring. Common isolated organisms were *Klebsiella pneumonia* ($n=8$, 44.4%) and *Pseudomonas aeruginosa* ($n=4$, 22.2%). Seventy-eight percent of children with recurrent UTIs secondary to VUR were on prophylactic antibiotics and more than 50% of children had renal scarring despite on prophylactic antibiotics.

CKD was the commonest complication seen in children with renal scarring ($n=13$, 27%). The median duration between the first detection of renal scarring and the diagnosis of CKD was one year (IQR=5.00 years). Six children with renal scarring (12.5%) developed hypertension with a median age of 10.5 years (IQR=6.00 years) at the first diagnosis. The median duration between the detection of renal scarring and the diagnosis of hypertension was one year (IQR=6.00). Five children (10.4%) developed proteinuria after the detection of renal scarring.
Table 1. Association between risk factors and development of renal scarring

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>Presence of renal scarring</th>
<th>χ² (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, n(%)</td>
<td>No, n(%)</td>
<td></td>
</tr>
<tr>
<td>Recurrent UTIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>27 (56.2)</td>
<td>23 (52.3)</td>
<td>0.146 (1)</td>
</tr>
<tr>
<td>- No</td>
<td>21 (43.8)</td>
<td>21 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Congenital anomaly of kidney and urinary tract (CAKUT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VUR</td>
<td>42 (91.3)</td>
<td>20 (66.7)</td>
<td>7.335 (1)</td>
</tr>
<tr>
<td>- Non-VUR</td>
<td>4 (8.7)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

UTI: Urinary tract infection, CAKUT: Congenital anomalies of kidney and urinary tract
VUR: Vesico-ureteric reflux
* p<0.05 is regarded as statistically significant
Chi-square test

Table 2 describes the association between risk factors and complications of renal scarring in children. There was no significant association between risk factors and outcomes of renal scarring in our population. Small number of our VUR children developed other complications of renal scarring. Five of them developed proteinuria while seven of them developed hypertension following renal scarring. However, as the number of children with proteinuria and hypertension were very small, the association between risk factors and proteinuria and association between risk factors and hypertension were not statistically evaluated.

Table 2. Association between risk factors and chronic kidney disease (CKD)

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>Chronic kidney disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, n(%)</td>
<td>No, n(%)</td>
</tr>
<tr>
<td>Recurrent UTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>7 (53.8)</td>
<td>20 (57.1)</td>
</tr>
<tr>
<td>- No</td>
<td>6 (46.2)</td>
<td>15 (42.9)</td>
</tr>
<tr>
<td>Congenital anomaly of kidney and urinary tract (CAKUT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VUR</td>
<td>15 (100.0)</td>
<td>47 (77.0)</td>
</tr>
<tr>
<td>- Non-VUR</td>
<td>0 (0.0)</td>
<td>14 (23.0)</td>
</tr>
</tbody>
</table>

UTI: Urinary tract infection; CAKUT: Congenital anomalies of kidney and urinary tract.
VUR: Vesico-ureteric reflux; CKD: Chronic kidney disease
*Fisher exact test

Discussion

The study has shown that about 50% of the requested DMSA scans were positive for renal scarring. Most children with scarring had VUR. Our results were comparable with other studies reported in Korea, Sweden, and Thailand which demonstrated a direct association between VUR and renal scarring [6,13,14]. Studies by Mei Ju Chern et al and Hae Sook Kim et al showed a significant association between high-grade VUR with renal scarring [1,15], but our cohort demonstrated that low grades of VUR conferred similar risks as high grade VUR.

Most of our VUR children had recurrent UTIs from organisms other than *E.coli*, mainly *Klebsiella pneumonia* organism. Our finding was comparable to the RIVUR trial and a study done by Shaikh et al. which showed a correlation between non-*E.coli* UTI in children with VUR and a higher proportion of abnormal DMSA scans [9,16]. We also demonstrated that two-thirds of VUR children developed renal scarring despite on prophylactic antibiotics. This could be due to high numbers of non-*E.coli* organism, resistance to the antibiotic used or to non-compliance to medication. Similar patterns were demonstrated in the RIVUR trial, which demonstrated that antibiotic prophylaxis did not prevent the development of renal scarring despite decreasing the risk of recurrent UTIs [16]. We demonstrated that some of the children with VUR developed renal scarring despite no history of recurrent UTIs. Potential reasons for this include either delay in seeking medical treatment by parents following febrile illness or under diagnosis of UTIs in young children by health care workers.

Our cohort also demonstrated that some of the children with recurrent UTIs developed renal scarring in the absence of VUR. This could be due to
spontaneous resolution of VUR. A study by Miguel et al. demonstrated that the chance of spontaneous resolution of VUR is higher with decreasing grade of VUR [17].

We also demonstrated that complications, such as hypertension and CKD manifested as early as one year from the detection of renal scarring. These findings highlight the importance of regular follow-up and blood pressure monitoring in order to prevent further deterioration of renal function.

Limitations

The findings of this study may not reflect the overall paediatric renal scarring population in Malaysia. The sample size was small and homogenous as majority were Malays in ethnicity. The results may also be biased by the referral patterns of the local paediatricians. Prospective studies with predefined standardised indications for DMSA scanning and including more centres in Malaysia may be needed to confirm our data.

Conclusion

The results of this study showed that a high proportion of DMSA renal scans showed the presence of scarring. Long term complications such as hypertension and CKD were demonstrated to occur as early as one year after the detection of the scarring.

Conflict of interest

No possible conflict of interest to be declared.

Acknowledgement

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References