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Original Research Article

A study to determine risk factors for renal scarring as detected by dimercaptosuccinic acid scan in children with urinary tract infection

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ABSTRACT

Background: The aim of the study was to determine the risk factors for renal scarring detected by DMSA (dimercaptosuccinic acid) scan in children with culture-proven urinary tract infection (UTI).
Methods: A hospital based observational case-control study was conducted from 2018 June to 2020 June in children aged between 1 month to 5 years who underwent a DMSA scan following culture-proven UTI (N=72). Of the children fulfilling the criteria, 43 had renal scarring in the DMSA scan as a case group and the remaining 29 children who had no renal scarring were taken as a control group.
Results: Of the total 72 cases with culture-positive UTI, 59% of patients had renal scarring and the rest and 40% were scar negative. There was no significant difference in the renal scarring observed with respect to age in the two groups. There was significant ($p<0.05$) the association noted between renal scarring and VUR (vesicoureteric reflux). A significant difference was observed in the renal scarring between the two groups regarding the presence of recurrent UTI ($p=0.000$). Although most cases (97.7%) had a fever in the DMSA positive group, this was not a significant risk factor for scarring ($p>0.05$). In DMSA positive group, circumcision was not a significant risk factor for scarring.
Conclusions: VUR and recurrent UTI were significant risk factors for renal scarring in children with culture-proven UTI as detected by DMSA scan. The other risk factors like age, sex, fever, leucocytosis and circumcision were not found to be significant.

Keywords: Urinary tract infection, Dimercaptosuccinic acid, Colony forming unit, Voiding cystourethrogram, Micturating cystourethrogram

INTRODUCTION

UTIs are common bacterial infections in infants and children. The risk of developing UTI before 14 years is approximately 1% in boys and 3-5% in girls. The incidence varies with age. During the first year of life, the male to female ratio is 3-5:1. Beyond 1-2 years, there is a female preponderance with a male to female ratio of 1:10. UTI diagnosis is often clinically missed in young children as symptoms are minimal and often non-specific. Identifying children with UTI who are at an increased risk of renal scarring is a major clinical challenge. Several complications of renal scarring have been reported including failure to thrive, hypertension, chronic renal failure and end-stage renal disease. Previous studies have shown that renal scarring was almost always associated with VUR.[1] Later studies using the DMSA scan, however, have suggested that scarring may often occur in the absence of VUR and it has been claimed that renal scarring may be independent of the presence or absence of VUR.[2,3] We therefore need to reassess our knowledge in this field based on studies in which acute pyelonephritis has been diagnosed and followed up with DMSA scans. Hence renal cortical scintigraphy with DMSA scan appears to be the best clinically applicable standard of reference for the diagnosis of renal scarring in children. Moreover, DMSA scan also provides an opportunity to study the progression of renal damage and

functional loss from the initial insult of acute pyelonephritis to the subsequent development of irreversible renal damage.[4] As per guidelines, all children between the ages of 1 month to 5 years with a culture-proven UTI will require a DMSA scan to detect renal scarring. But this is not practically possible due to the less availability and affordability of nuclear scans in a resource-limited setting like India. The main aim of this study was to identify those children who were at more risk of developing renal scarring following UTI so that more emphasis can be given to those who had a definite risk for developing renal scarring and complications.

Aim

The aim of this study was to determine the risk factors for renal scarring detected by DMSA scan in children with culture-proven UTI.

METHODS

The hospital based observational case-control study was conducted at the department of pediatrics, GITAM institute of medical sciences and research, Visakhapatnam, Andhra Pradesh and Giggles by Omni RK women and children's hospital, Visakhapatnam. The institutional ethical committee approved the study. Informed written consent was obtained from at least one parent of each patient before enrolment.

Duration of the study

The duration of the study was 2 years from June 2018 to June 2020.

Sample population

Children aged between 1 month to 5 years of age who underwent DMSA scan following culture-proven UTI were the sample population.

Inclusion criteria

All the children aged between 1 month to 5 years of age who underwent a DMSA scan following culture-proven UTI were included in the study.

Exclusion criteria

Children with culture-negative UTI, children with asymptomatic UTI and children with genitourinary anomalies were excluded from the study.

Sample size and sample technique

The required sample size for this study was calculated using the formula,

$n=\frac{\{(Z\alpha+Z\beta)^2 2Pq\}}{d^2}$,

where,

n is the required sample size,

Zα=1.96, (z value for an α error of 5%),

Zβ=0.84 (z value for an β error of 20%),

$P=\frac{(p1+p2)}{2}$,

p1 is the percentage of cases exposed to a risk factor,

p2 is the percentage of control exposed to a risk factor,

q=(100-P),

d=(p1- p2),

here p1=55%, p2=20% are assumed.

Thus, we are expecting an N value of 30 each in case and control group. But in the present study we got only 29 cases and 43 controls.

Study methods

Data collection technique and tools

Baseline data like age, sex, symptoms like fever, details of laboratory investigations like total count, micurating cystourethrogram, history of recurrent UTI and circumcision were collected after the direct interview of parents and from pediatric case records. Definition of UTI used for the purpose of the study (Table 1).

Table 1: Criteria for the diagnosis of UTI.

Method of collection	Colony count	Probability of infection (%)
Suprapubic aspiration	Any number pathogen	99
Urethral catheterization	$>10^5$ CFU/Ml	95
Midstream clean catch	$>5\times10^4$ CFU/ml	90-95

Here 72 children with culture-proven UTI who underwent DMSA, the scan was included in the study. 13 children who had culture-negative UTI were excluded from the study. Of the children fulfilling the criteria, 43 had renal scarring in the DMSA scan, hence the case group and the remaining 29 children, who had no renal scarring were taken as control groups.

The comparison was made between these two groups with respect to the following variables: (1) age: 1 month

to 1 year and 1-5 years of age; (2) sex; (3) fever: present/absent; (4) lab factors like TC is normal/leukocytosis, MCU-VUR is present/absent; (5) history of recurrent UTI is present/absent and (6) circumcision is done/not.

Urine investigations were done at the time of presentation, that is, before starting antibiotics. A clean-catch midstream specimen was used to minimize contamination by periurethral flora. Antiseptic washes and forced retraction of the prepuce was not done. In infants, urine sample was obtained by either suprapubic aspiration or transurethral bladder catheterization. The urine specimens were plated within one hour of collection. Details of DMSA scan done following culture-positive UTI were collected from the nuclear medicine department.

Statistical analysis

Data were recorded on a predesigned proforma and managed on an excel spreadsheet. Comparative analysis of variables of the two groups were done using the Chi square test or Fisher's exact test to examine the association. A difference with a significant level <0.05 was considered statistically significant. Statistical analysis was done by using SSPS 15.0 version.

RESULTS

The number of culture-negative UTI cases excluded from the study were 13. The number of culture-positive UTI cases undergone DMSA scan were 72. The prevalence of DMSA-positive cases in our study population was 59.72% (N=43). DMSA was negative in 40.28% (N=29) cases.

Association between DMSA and age

Of total 72 children, 65% were >1 year (1-5 years) and 35% were <1 year (1 month to 1 year). The age distribution ratio was 1.8:1. Among DMSA-positive cases, 60% were of age >1 year and rest 40% were <1 year of age, with age distribution of 1.5:1. In DMSA negative cases, 72% were of age >1 year and rest 28% were <1 year of age, with age distribution of 2.5:1.

Association between DMSA and sex

Of 72 children, 51% were males and 49% were females. The sex ratio was 1.05:1. Among DMSA-positive cases, 55.8% were males and the rest, 44.2%, were females. Among DMSA-negative cases, 55.2% were males and rest 44.8% were females. Therefore, in the present study, DMSA-positive and DMSA-negative cases had same-sex ratio of 1.2:1.

Table 2: Statistical analysis of association of DMSA and age, sex, fever, leukocytosis, recurrent UTI, VUR and circumcision.

Statistical analysis	DMSA			x^2	P value
	Negative (%)	Positive (%)	Total (%)		
Age (in years)					
<1 cases	27.6	39.5	34	1.091	0.296
> 1 cases	72.4	60.5	66		
Gender					
Male	55.2	44.2	50	0.837	0.36
Female	44.8	55.8	50		
Fever					
Negative	6.9	2.3	5	0.906	0.561
Positive	93.1	97.7	95		
Leukocytosis					
Normal	96.6	69.8	83	7.932	0.005
High	3.4	30.2	17		
VUR					
Negative	45.3	35.8	41	5.658	0.017
Positive	54.7	64.2	59		
Recurrent UTI					
Negative	51.7	2.3	27	24.252	<0.001
Positive	48.3	97.7	73		
Circumcision					
Negative	69.2	62.5	66	0.168	0.734
Positive	30.8	37.5	34		

Association between DMSA and fever

Of 72 children, fever was present in 95% of cases. The majority of DMSA-positive (97.7%) and DMSA-negative cases (93.1%) had fever.

DMSA and leukocytosis

Among 72 children, 80.6% had normal count and 19.4% had leukocytosis. In DMSA-positive cases, 30.2% had leukocytosis and 69.8% did not have. In DMSA-negative cases, 96.6% did not have leukocytosis, only 3.4% had it.

DMSA and recurrent UTI

Of a total of 72 children, recurrent UTI was positive in 77.78% of cases. The majority of DMSA-positive cases (97.7%) had recurrent UTI. In DMSA-negative cases, recurrent UTI present in 48.3%, absent in 51.7%.

DMSA and VUR

Among 72 cases, VUR was positive in 33.3%. In DMSA-positive cases, 64.2% had VUR, 35.8% didn't have it. In DMSA-negative cases, 54.7% had VUR, 45.3% did not have it.

DMSA and circumcision

Among 37 males, circumcision was done in 35.1%. In DMSA-positive cases 37.5% were circumcised, 62.5% were uncircumcised. In DMSA-negative cases, 30.8% were circumcised, 69.2% were uncircumcised.

Statistical analysis

Renal scarring was more observed in children without leucocytosis and this difference was statistically significant. Renal scarring was more observed in children with VUR, the difference was statistically significant ($p<0.05$). Renal scarring was more observed in children with recurrent UTI, the difference was statistically significant ($p<0.05$) (Table 2).

DISCUSSION

Identifying children with UTI who are at increased risk of renal scarring is a major clinical challenge. Several complications of renal scarring have been reported, including failure to thrive, hypertension, chronic renal failure and end-stage renal disease. Renal scars are present in 6.1% children with UTI.[5] The first episode of UTI in infants should be investigated and followed up well to prevent renal scarring later.[6] The advantages of using 99mTc-DMSA renal scintigraphy to evaluate renal scarring have been confirmed in various studies.[7-9] They demonstrated the efficiency of this imaging modality for clinical use compared to conventional imaging techniques such as ultrasound, CT and MRI methodology.

The present study analyzed seven risk factors for renal scarring in children with culture-proven UTI, age, sex, symptoms like fever, details of laboratory investigations like total count, micurating cystourethrogram, history of recurrent UTI and circumcision. The study group consisted of 72 children with culture-positive UTI, of which DMSA scan showed scar positivity in 59% cases and the rest 40% cases were scar negative. The prevalence of renal scarring in the present study was 59.72%, comparable to other studies (59.7% in the present study and 50-60% in different studies).

Sex distribution

The sex ratio in the present study group of 72 children was 1.05:1. But both DMSA-positive seven negative cases had a same-sex ratio of 1.2:1, a slightly higher number of males than females. The prevalence of renal scarring was almost equal in males as compared to females, which was comparable with studies by Ditchfield et al and Fahimeh et al.[5,10] In our study, the incidence of culture-positive UTI in the age group between 1 month to 1 year was found to be more in males and in 1-5 years more in females.

Age distribution

The age distribution ratio in the present study was 1.8:1, for the study group of 72, with more children of age 1 month to 1 year. The age distribution in DMSA-positive cases were 1.5:1 and DMSA-negative cases 2.5:1, with more children belonging to age group 1-5 years. The prevalence of renal scarring was found to be more in age 1-5 years as compared to infants of age 1 month to 1 year, but this was not found to be statistically significant. A study by Panahi et al showed a significant association between renal scarring and infants <1 year of age.[11]

Fever

The present study has supported the earlier studies done by Rushton et al and Jacobson et al with respect to the presence of fever as a risk factor for renal scarring.[12,13] In our study, 97.7% of children who had significant renal scarring had fever, but this was not found to be significant with a $p=0.561$. A study by Ehsanipur et al in 2009 revealed a significant association between duration of fever and renal scarring.[9]

Leucocytosis

Ehsanipur et al studied the risk factors of renal scarring in 80 children, 52% of them showed leukocytosis, but there was no significant association obtained between the two, with a p value of 0.96.[9] In the present study, leucocytosis was found in 30% of cases with renal scarring but in the remaining 70% cases did not have any leukocytosis and the association was not found to be significant. This can be attributed to the antibiotics, many of these patients would have received before the referral.

VUR

In our study, 44.2% of children with renal scarring had positive VUR. In the present study, renal scarring was observed in a significantly greater proportion of patients with positive VUR compared with those without positive VUR (p=0.017). But here, 44.2% of children with renal scarring had positive VUR and in the rest, 55.8%, VUR was absent. This implicates not only the presence of VUR, but the grade of VUR, time lag for any intervention, route and efficacy of antibiotics, all added up to the formation of renal scarring.

Recurrent UTI

Ehsanipur et al in 2009 had studied the association of recurrent UTI as a risk factor of renal scarring in 80 children of age group 1 month to 5 years. Recurrence of UTI occurred twice and thrice in 25 (31%) and 11 (13.8%) children respective. A significant association was found (with a p=0.001) between recurrent UTI and renal scarring. Lee et al, Mir et al supported this study.[14,15] In their study, children with three/more than three episodes of UTI were considered as recurrent UTI cases and included in the study. This study also concluded recurrent UTI as a significant risk factor for renal scarring. In this present study, 97.7% of children with renal scarring had history of recurrent UTI, while only a minority of 2.3% didn't have that history. Our study also showed that 52 % of scar negative children did not have recurrent UTI, while the rest of 48% cases had history of recurrent UTI. This implicates that in the presence of recurrent UTI, the risk for developing renal scarring is much high compared to those without recurrent UTI. The risk for renal scarring is slightly less in the absence of recurrent UTI compared to those with recurrent UTI.

Circumcision

The ratio between the circumcised and uncircumcised is 1:1.8, more children being uncircumcised. In children who had undergone circumcision, the occurrence of renal scarring was found to be 30%, while in uncircumcised children it was 37,5%, the association was not found to be significant (p=0.73). This study was comparable with studies by Wiswell et al supported this.[16] In these two studies also no significant association between circumcision and UTI were obtained. In addition to the studied factors, some other risk factors largely account for the development of renal parenchyma scarring including the route of antibiotics administration, the time elapsed before the onset of symptoms and initiation of therapy.[17] Though we did not evaluate in this study, it has been observed that other factors such as bacterial virulence, immunodeficiency, and anatomic or functional abnormalities make children with UTI vulnerable to renal scarring.[18]

Limitations

Limitations of this study were small sample size, culture negative UTI were excluded, Affordability and availability of DMSA scans for all children with culture-proven UTI and resource-limited setting.

CONCLUSION

VUR and recurrent UTI were significant risk factors for renal scarring in children with culture-proven UTI as detected by DMSA scan. Compared in this study, the other risk factors like age, sex, fever, leucocytosis and circumcision were not found to be significant.

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