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The outcome and the renal status of children at least five years after an initial diagnosis of primary vesicoureteral reflux

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Introduction

Vesico-ureteral reflux (VUR) is the retrograde flow of urine from the bladder into the upper tracts (ureters and renal pelvis). It is a congenital condition and mostly familial[1]. International Reflux Study Classification is used to grade the severity of VUR. Grade I and II indicate mild VUR without the dilatation of ureter. Grade III –V indicate severe VUR with dilatation of ureter. [1]

The prevalence of VUR is uncertain[1, 2]. *Sargent et al* reported a prevalence of 0.4-1.8% in children without Urinary Tract Infection (UTI) [3].However, VUR is found in 30% of children presenting with urinary tract infections which clearly indicates the increased risk of UTI in children with VUR [4, 5]. Stagnation of urine due to VUR may lead to increased risk of UTI/ pyelonephritis. Moreover the risk of developing renal scarring is more than 30% (30-49%) in a child with VUR complicated with UTI [6].

In addition to predisposition for pyelonephritis and renal scarring, VUR is postulated to cause renin induced young hypertension and renal damage [1, 7]. Yet, some researchers present evidence challenging this theory. They believe most kidney defects are congenital (congenital dysplastic) and doubt the impact of VUR in new renal scar formation and predisposition to UTI[8] .This theory has led to dramatic change in investigation protocols searching for VUR.

However, there is well defined evidence for reflux nephropathy causing renal damage and scarring. *Ransely et al* in 1978 demonstrated this using an animal model. They induced unilateral VUR and introduced pathogenic bacteria to the bladder. They found that whenever a UTI occurred in those animals with VUR, the kidneys got scarred consistently. These scars were similar to the scars seen in children secondary to reflux nephropathy morphologically, histologically and on DMSA.(9) Furthermore, the authors demonstrated that the process of scaring can happen within the space of days[10] .Most of the long term follow up studies have revealed a high rate of renal failure in children with high grade VUR [11] .In most renal transplant programs in developed countries, 10-15% of transplantation has been for reflux nephropathy which highlights the importance of diagnosis and proper follow up of VUR[12] .Therefore, VUR is not a benign condition and needs prompt diagnosis, treatment and follow up[13].

In Sri Lanka, there is a high rate of under diagnosis of childhood UTI due to improper use of antibiotics without screening for UTI. Therefore first documented UTI may not be the very first episode. In addition, congenital anomalies are detected late due to the absence of properly established intra uterine anomaly scanning. Therefore there is a high chance of late presentation of children with VUR with complications such as renal scaring and hypertension**.**

Due to these facts, local guidelines need to be formulated to facilitate early detection of VUR and proper follow up. For this process we believe it is important to have our own data on complications and its long term outcome. Only a very few research attempts have been undertaken in Sri Lanka to assess the clinical pattern and outcome of VUR.

A prospective study done from 2014 to 2016 by *Jayantha UK et al,* analysed 143 infants with febrile UTI. They detected VUR in 32% of cases. Interestingly, 70% of the patients with high grade VUR had normal ultra sound scan. Therefor they have highlighted the importance of MCUG as a diagnostic tool[14] .

Abeysekara CK et al have done a prospective study consisting of 56 children where 35% had grade I to II VUR and 65% had grade III to V VUR. Interestingly, 55% had detectable renal scarring.17% had breakthrough UTI while on treatment. Except for single patient having high systolic pressure and one having proteinuria, No other long term clinical problems were identified in the study[15].

Methods

Objectives

- To evaluate long term renal outcome of children with Vesico-ureteral reflux and to compare the renal outcome of dilating VUR and with the non-dilating VUR.
- To evaluate the status of dilating VUR after at least 5 years follow-up

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- To evaluate the effect of VUR to the renal growth by measuring the renal volume using the ellipsoid formula

Study setting , design and period

This study was a retrospective cohort study spanning from 2020 to 2021, conducted in the Renal Clinic of the Pediatric Professorial Unit at Teaching Hospital Karapitiya. The cohort consisted of sixty-seven (67) patients diagnosed with primary vesicoureteric reflux (VUR), all of whom received ongoing care at the Renal Clinic Paediatric Professorial Unit, Teaching Hospital Karapitiya. Initial enrollment of participants occurred in 2020, and comprehensive data collection and measurements were done throughout the duration of 2020 to 2021. The cohort contained thirty-four patients with grade 1-2 VUR and thirty-three patients with grade 3 and above.

The study sample contained individuals with VUR who had been under clinic surveillance for a minimum of 5 years, extending up to a maximum follow-up duration of 10 years. Notably, patients with secondary causes contributing to VUR, such as Posterior Urethral Valve, neurogenic bladder, or cystocele, were excluded from the study.

The sample size for this study was calculated using "Kane SP. Sample Size Calculator". (Clin Calc: https://clincalc.com/stats/samplesize.aspx.Updated July 24, 2019).

The prevalence of renal scaring was taken as 61% for dilating VUR and 27% for non-dilating VUR.[18].Alpha error was taken as 0.05% and power was 80%.The minimum sample size calculated was 64 patients.(32 patients for each group).

Method of Data Collection

The demographic details were obtained using a pre tested interviewer –administered questionnaire. The patient data was collected and analyzed in 2 groups: mild VUR (grade I and II) and high grade VUR (grade III – V).If a patient presented with bilateral VUR with 2 different gradings, he/she was included to the category of highest grading. The follow up clinic notes were referred to obtain the history of UTI, etiology for UTI, follow up anthropometric measures (height), biochemical (Early morning urine for micro albumin and serum creatinine) and radiological investigations (Ultra Sound Scan, MCUG and DMSA).

Investigators obtained anthropometric measurements. The height was measured to closest 0.1cm using a Stadiometer. The weight measurements were taken to the closest 100g using an electronic weighing scale. The standard formula (weight in kilograms/height in meters2) was used to calculate the Body mass index (BMI). The World Health Organization (WHO) growth charts were referred for the interpretation of anthropometric measurements. Blood pressure was obtained from the right arm after 15 minutes in sitting position.

Urine was checked for early morning micro-albumin urea when they were free of urinary tract infection. Venous blood sample was taken for serum creatinine. Venipuncture was carried out by an experienced nursing officer at professorial paediatric unit.

A full bladder Ultra sound scan was carried out by an experienced single radiologist using a standard device and a probe. Renal length, width, antero-posterior diameter was measured in both kidneys. The persistence of VUR was accessed by the evidence from ultra sound scan.

Data interpretation and analysis

The following parameters were used to measure the renal outcome.

- Elevated Blood pressure
- Presence of micro-albumin urea in early morning sample
- Calculated e-GFR using modified Swartz formula
- Presence of small kidneys in Ultra sound scan
- DMSA evidence of renal scaring

Blood pressure readings higher than 95th centile for age, sex and height centile was considered as hypertensive. In addition patients who were already on anti-hypertensive treatment was considered as having hypertension

Kidney volume was calculated using the ellipsoid formula[16]. (Kidney length x width x AP diameter x 0.52). The calculated renal volume was divided by body surface area to normalize the effect of body size. Body Surface Area related renal volume is normally distributed irrespective of body size and side of the kidney from birth to 18 years[17]. The mean relative volume of a kidney is considered as 66ml/m2 and normal range is considered as 85ml/m2 to(90th percentile) to 45ml/m2(10th centile) [17]. A kidney was considered small if kidney size was less than 45ml/m2 irrespective with the age.

Stunting was defined as height for age <-2SD. BMI between -2SD to -3SD was considered as thinness and < -3SD as extreme thinness. Data were analysed using SPSS 25.0 .The Chi-square test was used to analyse data. The significance of the p-value was considered as 0.05.

Ethical approval for this study was taken from Ethics review committee of the Sri Lanka College of Paediatricians.

All participants were enrolled on voluntary basis. The nature of the study was explained to all participants clearly. The informed written consent from the parents

and assent from the participants were obtained prior to any data collection. All patient data including patient identity were kept confidential at all times. Patient information were handled with a numerical code instead of names. Only the researcher had the access to these data.

Results

The total number recruited to the study was sixty seven patients. Out of sixty seven, 49% (n= 33) were males. The mean age of the sample was 101.05 (±36.2) months. Ninety seven per cent (n=65) were belonging to Sinhala ethnic group, while 3% (n=2) were Muslims. Thirty four (51%) patients had grade I-11 VUR. All the patients in the study had at least a single urinary tract infection (UTI). However, 40% (n = 27) of children had 2 or more episodes. The group with severe VUR had recurrent UTIs in 48% (n=16) of patients where as other group had recurrent UTIs in 32% (n=11). However the two groups did not show statistically significant difference in predisposition to recurrent UTI (Chi square =1.8114, p value= 0.1783). The incidence of scarring in total study population was 44.7%. (n=30).

The most common causative agent for the UTI was Escherichia coli. Eighty nine per cent of the documented culture positivity was due to coliform organisms.

Table 1. *Characteristics of the total study group*

Variable	Number (Percentage)
Sex	
Male	33 (49.2%)
Female	34 (50.7%)
Age	
>8 years	36 (53.7%)
8-12 years	23 (34.3%)
>12 years	08 (11.9%)
History of UTI	
Single	40 (60%)
2 or more	27 (40%)
Age at first documented UTI	
<1 year	39 (58.2%)
1-2 years	22 (32.8%)
>2 years	06(8.9%)
DMSA findings	
U/L Scarring	25 (37.3%)
B/L Scarring	05 (7.46%)
No Scarring	37 (55.2%)
MCUG findings	
Right side VUR	16 (23.8%)
Left side VUR	23 (34.3%)
Bilateral VUR	28 (41.7%)
Severity of VUR	
Grade I-II	34 (50.7%)
Grade III-V	33 (49.2%)

Renal scaring was present in 20.6% (n=7) of patients among mild VUR group, where as 69.7% (n=23) had renal scarring in severe VUR group. The two groups showed a significant difference in the incidence of scarring and higher grade VUR had significant predisposition to scarring. (Chi square 16.33, p value 0.000147).

Out of 67 patients, only 42 patients were available for all the imaging studies and investigations. Rest of the patients were defaulted during the Covid -19 outbreak. Among 42 children, 54.8% (n=23) were females, and 52.4% (n=22) had Grade III-V VUR (severe). The mean age of the Grade I-II VUR (mild) group was 95.40 (±30.6) months, whereas the other group had a mean age of 103.4 months (±45.9).

There was no significant difference in stunting (p=0.3166) and thinness (p=0.1157) among mild VUR and Severe VUR groups respectively (table 02).

Microalbuminuria was observed in 22.7% (n=5) in the severe VUR group and 25% (n=5) in the mild VUR group. Among patients with higher VUR, 9% (n=2) had hypertension, and 13.6% (n=3) had elevated creatinine. No patient with mild VUR suffered from hypertension. More than half, 54.5% (n=12) patients with severe VUR had persistent ultrasonographic evidence of reflux, which was statistically significant compared (p=0.0022). The severe VUR group had 31.8% (n=7) at least one small/ contracted kidney, whereas 25% (n=5) of children with mild VUR also showed small kidney. (p=0.6251). Furthermore, renal scarring of at least one kidney was present in 63.6% (n=14) with severe VUR compared to 25% (n=5) in the mild VUR category (p=0.0276).

The kidney volumes of all the patients were measured during the study. The figure 01 illustrates the mean kidney volumes of participants. The mean volume of normal left kidney and right kidney were 74.29cm^3/m^2 and 66.83cm^3/m^2 respectively. The mean size of kidneys affected by VUR was smaller than the normal kidneys. Scarred kidneys were found to be significantly smaller. The kidneys with an opposite side scarred kidneys were comparatively larger than the normal kidneys likely due to compensatory hypertrophy.

3. Discussion

The main aim of this study was to evaluate long term renal outcome of vesico ureteral reflux. The higher grade VUR had significant risk of scarring than lower grade VUR.

The incidence of scarring in our study population was 44.7% (30/67). The severe VUR group had incidence of 69.7% scarring whereas 20.6% in mild VUR group. These findings were compatible with most other studies worldwide.

Mir S et al in 2013 studied the incidence of renal scarring among patients with primary VUR. The incidence of

renal scarring among patients with primary VUR in their study was 48.9%. The cumulative incidence of scarring for grade I and II Vesico-ureteric reflux was 27% whereas for grade III and above, it was 61 % [18] .Shah KJ et al in 1978, in a similar study to Mir S et al, found that the incidence of renal scaring in primary VUR was 53%. In this study, the incidence of renal scarring in children with non-dilating VUR was 25.5% (11/43) whereas for dilating VUR it was 79%(37/47) [19].

Table 2. *Long term outcome of the study population*

Parameter	Grade I-II VUR (n,%)	Grade III-V VUR (n,%)	Chi Square value	P value
Stunting	1 (5%)	3 (13.6%)	1.0029	0.3166
Thinness	3 (15%)	8 (36.4%)	2.4734	0.1157
Microalbuminuria	5 (25%)	5 (22.7%)	0.0298	0.8628
High serum creatinine	1 (5%)	3 (13.6%)	0.9068	0.3409
Ultrasonic evidence of Persistence of VUR	2 (10%)	12 (54.5%)	9.3545	0.0022
Contracted kidney (renal volume <10th centile)	5 (25%)	7 (31.8%)	0.2386	0.6251
Scarring in DMSA	5 (25%)	14 (63.6%)	6.3127	0.0276

The previous Sri Lankan study done by Abeysekara et al revealed a incidence of 55% renal scaring in their study group. However their study group was consisted of 56 children and 65% of the population had grade III to V VUR.

With regard to other long term complications, microalbuminurea was reported in 23% of patients (10/42) in our study. Hypertension was found only in 2 patients (4.7%). Both of them had severe VUR. *Smellie JM et al* reported a follow up study of 10-41 years in 216 adults in 1998. The researchers detected 17 adults with hypertension and/or raised proteinuria. Those with complications had extensive renal scarring in childhood and/or borderline high blood pressure in childhood [20] .These findings highlight the importance of early detection and proper follow up which could prevent the complications of VUR.

There was no significant difference between 2 groups with regard to growth parameters.

In our study, we have looked into the ultrasonic evidence of persistence of VUR. This was done with a full bladder Doppler ultrasound scan. 90% (n=18) of patients who had initial diagnosis of mild VUR had evidence of resolved VUR after 5 years, whereas 45.5% of patients with severe VUR had evidence of persistent disease which was statistically significant. These figures were similar to Arant BS who reported the results of 5 year prospective follow up study of infants and children younger than 5 years in 1984. In his study, Eighty two per cent of grade 1 VUR and 80% of grade II VUR resolved while only 43% of grade III VUR resolved [21].

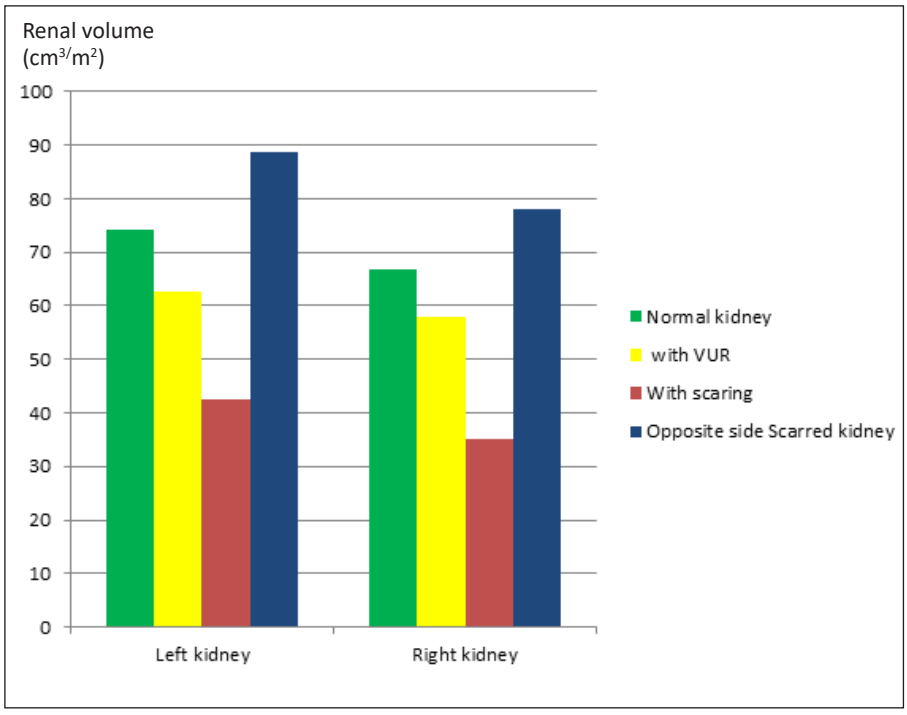

Figure 1.Renal volume measurements (cm^3/m^2)

The growth of the kidney is another important aspect in the monitoring of patients with VUR. Twenty eight per cent (n=12) of patients in our study showed poor kidney growth that is less than 10th centile.

Hanna RL et al in 2011 studied the association of adult kidney size with childhood VUR. They have shown kidneys with a history of VUR were 12% smaller than those without VUR. Furthermore; the researchers claimed even low grade VUR can cause long term sequence[22] . In our study the kidneys with VUR showed a mean volume which is comparatively smaller than the normal kidneys. However, further studies are required to confirm the relationship

between the small kidney and primary VUR since there are other confounding factors in this analysis.

The size difference was further prominent in kidneys with scarring compared to the normal kidney. Moreover, the renal volumes also demonstrated the effect of small scared kidney and compensatory hypertrophy of the opposite kidney.The mean renal volume in the study population was compatible with the figures of study done by Scholbach TH, Weitzel D et al [17].

Limitations

The study was carried out during the period of covid -19 pandemic. During this period, there were lot of restrictions on travelling and patient care. The clinic attendance was also dropped drastically. We have taken all the necessary health measures to prevent the spread of the virus. However a significant number of participants were lost to the follow up during the study period. As a result, we were only able to complete the data collection in forty two (42) patients. We consider this as a significant limitation to the study.

Conclusions , recommendations

Both higher grade and lower grade VUR can result in long term renal damage, microalbuminuria, and small contracted kidneys. However, the higher grade VUR had significant risk of scarring than lower grade VUR. Furthermore, higher grade VUR is associated with higher chance of persistent VUR. There was no association found between the severity of VUR and chance of recurrent UTI.

Primary VUR can have an impact on the growth of the kidneys. However, further studies are required to confirm the association.

Unfortunately, significant percentage of the study population was lost to the follow up during the study which can impact on these conclusions.

The early identification and monitoring of VUR will be important in preventing its complications. Implementation of proper antenatal scans to detect antenatal renal pelvis dilatation in all pregnancies will help early identification of VUR. It is also important to introduce a new national guideline for imaging and management of urinary tract infections in infants as the current Sri Lankan guidelines are out-dated.

Measurement and calculation of renal volumes can be used to monitor the growth of the kidneys with VUR and scaring. Patients with VUR should be monitored until their adolescence or beyond as VUR can result in long term complications irrespective of its severity.

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