

Outcome of Vesico -Ureteral Reflux (VUR) in Children associated with Urinary Tract Infection (UTI)

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Abstract

Background & Methods: The aim of the study is to study Outcome of Vesico -Ureteral Reflux (VUR) in Children associated with Urinary Tract Infection (UTI). The data included necessary laboratory investigation reports, hematological, clinic-pathological, microbiological and radiological parameters.

Results: Out of 60 bilateral refluxing ureters, males accounted for 17 (34 VUR) and females being 13 (26 VUR). Among the 17 male children, 4 children (23.52%) had different grades of VUR on either side compared to 15.38% (2 out of 13) in females.

Conclusion: Children less than 3 years of age are at higher risk of VUR after UTI, hence test like USG Abdomen, MCUG, DMSA should be done once the infection is controlled. Older children with UTI should undergo DMSA scan. Understanding the prevalence pattern, detection of early signs of disease and complications is crucial in administering appropriate treatment to minimise complications. This will further aid in providing appropriate management in cases of VUR according to severity.

Keywords: Vesico, Ureteral, Children, Urinary & Infection.

Study Design: Observational Study.

Introduction

Urinary Tract Infection (UTI) is one of the common diseases in pediatrics practice and it causes harmful effects on renal tissue [1]. In the first century AD, Galen first described unidirectional flows of Vesico ureteric valve. Hutch in 1952 narrated the causal relation between reflux and pyelonephritis in paraplegics. It was also noted in a study with pigs, scarring in renal tissue in the absence of infection but occurred rapidly when the infection was present. In 1978 Ramsley and Ridsen showed that vesico ureteric reflux (VUR) and UTI are both prerequisites for development of renal scar. They also emphasized the importance of non-refluxing (conical) papilla which acts as valves occluding duct orifices when renal pelvic pressure increases thus protecting kidneys from Reflux Nephropathy (RN) [2].

Primary VUR is the most common hereditary disorder of genito-urinary tract transmitted most commonly as autosomal dominant inheritances. UTIs are primarily caused by E. coli max seen in 75-90% of all infections in girls [3]. Other organisms responsible are Klebsiella, Proteus, Staph. Saprophyticus and Enterococci. Adenovirus and other viral infections are associated with cystitis and gross haematuria [4].

Depending upon the severity of UTI, VUR may occur unilaterally or on both sides [5]. Differential renal function (DRF) of $< 45\%$ is considered abnormal and these functions differ depending on the severity of VUR and unilateral/ bilateral VUR [6]. There has been scanty literature on unilateral/ bilateral VUR and renal function in UTI. Hence the exercise was undertaken to study these aspects among children of Armed forces personnel and those admitted in tertiary care hospital.

Material and Methods

The observational study was conducted from August 2017 to December 2020 in teaching military hospital. The study was approved by Institutional ethics Committee and informed consent was taken from each parent before inclusion in the study.

The demographic, prehospital data, clinical history and examination details of enrolled children were entered in a predesigned structured proforma. The data included necessary laboratory investigation reports, hematological, clinic-pathological, microbiological and radiological parameters. Ultrasonography (USG) of abdomen was done for evaluating kidney and bladder including assessment of pelvic and calyceal dilatation. Contrast voiding cystourethrogram (VCUG) is performed for analyzing more anatomical information such as duplex collecting system, ectopic ureter, para-ureteral bladder diverticulum, bladder outlet obstruction in boys and spinning top urethra in girls. Dimercaptosuccinic acid (DMSA) scintigraphy is done to detect renal abscess, cysts, duplex kidney and hydronephrosis. Diehthylene triamine penta-acetic acid (DTPA) scan is performed to detect function of each kidney as percentage.

Inclusion criteria:

- a) Children aged 01 month - 12 years with VUR due to UTI.
- b) Parents willing to provide written informed consent.

Exclusion criteria:

- a) Children with antenatally diagnosed renal disease.
- b) Children with chronic diseases who were bedridden for a long time or who were on diuretic or corticosteroid/ immunosuppressants.
- c) Children with pelviureteric junction abnormalities.

Sample size:

Assuming a level 12% of children with UTI develop VUR, number of children required is minimum of 160 children. The estimate is derived by using the following formula: $N = Z_{\alpha/2}^2 P(1-P) / \epsilon^2$ $Z_{\alpha/2}$ factor corresponds to Type I error and was taken as 1.96 with two-sided test P is % of children with UTI developing VUR (assumed as 12 % from hospital data) 1-P is children with UTI not developing VUR ϵ^2 is the level of precision (usually taken as 5%) $N = 1.96 \times 1.96 \times 0.12 \times 0.88 / 0.5 \times 0.5 = 160$ children

Grading of VUR:

- Grade I: VUR into non dilated ureter
- Grade II: VUR into upper collecting system without dilatation
- Grade III: VUR into dilated ureter and or Blunting of calyceal fornices
- Grade IV: VUR into grossly dilated ureter
- Grade V: Massive VUR with significant ureteral dilatation and tortuosity with loss of papillary impression

Statistical analysis:

The data for study was collected in pre-designed study proforma and was verified for completeness and consistency before transferring into MS Excel for further analysis. Univariant analysis was done between survivors and on survivors. The continuous variables were expressed as mean and standard deviation (SD), median and inter-quartile range (IQR) and frequency distribution for categorical variables. Non parametric tests like Man-Whitney Median tests, Chi-Square and Fishers exact test are applied when necessary. Subgroup analysis is applied between various factors and outcome measures. p-value of < 0.05 was considered statistically significant. Data was analysed using SSPS (20th Version).

Result

A total of 403 children with UTI were analysed after excluding those not willing to participate, having congenital structural anomalies, not willing to give consent and lost to follow up. The results are narrated in the subsequent paragraphs. Table 1: Number of cases studied (N = 403).

Table 1: Age and Gender wise distribution of study group (N = 403).

Gender	Male	Female	Total
Number (%)	222(55.08)	181(44.91)	403(100)

Males predominant with M:F ratio of 1.22:1.

Table 2: Prevalence of VUR patients according to age and gender (55).

Age		Study Group	
	Number %	Male %	Female %
1–36 months	270(66.99)	151(59.63)	111(40.36)
>36-108 months	124(30.76)	48(44.35)	64(55.64)
>108-144 months	9(2.23)	3(33.33)	6(66.66)
Total	403(100)	222(55.05)	181(44.99)

Majority (66.99%) were in the age group of 1-36 months. Male children constituted majority (59.63%) in this group.

Age (months)	Number (%)	Male Number (%)	Female number (%)
1-36 months	41/55 (74.54)	24/41 (58.55)	17/41 (41.45)
>36-108 months	11/55 (20)	4/11 (36.36)	7/11 (63.63)
>108-144 months	3/55 (5.45)	1/3 (33.33)	2/3 (66.66)
	55/403 (13.64)	29/55 (52.72)	26/55 (47.27)

Total 403 children of UTI were studied. 55 children (13.64%) had VUR. Out of 55 majorly (74.54%) were in the age group of 1-36 months and also males were predominant (58.57%). Thus, prevalence of VUR in both genders were in the ratio of 1.11:1.

Table 3: Prevalence of unilateral and bilateral VUR according to gender (N=55):

VUR (number)	Males number (%)	Females number (%)
Bilateral (30)	17/30(56.66)	13/30(43.33)
Unilateral (25)	13/25 (52.00)	12/25 (48.00)

Out of 55 children with VUR, 17 male children (56.66 %) and 13 female children (43.33%) had bilateral VUR, whereas 13 out of 25 male children (52%) and 12 out of 25 female children (48%) had unilateral VUR. Thus, there were 85 refluxing ureters (47 in males and 38 females) with M:F ratio of 1.27:1.

Table 4: Grades of VUR according to gender among total number of refluxing ureters

(N=85):

Grades of VUR	Refluxing ureters Number (%)	Males Number (%)	Females Number (%)
Grade I	0	0	0
Grade II	37 (43.52)	23/37 (62.16)	14/37 (37.83)
Grade III	20 (23.52)	8/20 (40.0)	12/20 (60.0)
Grade IV	18 (21.17)	8/18 (44.44)	10/18 (55.55)
Grade V	10 (11.76)	8/10 (80)	2/10 (20)

TOTAL	85(100)	47/85 (65.29)	38/85 (44.70)

There were total of 85 refluxing ureters. Majority (55.29%) were males. Grade I VUR was found to be more (43.52%) among all the grades as well as in males among them (62.16%).

Table 5: Differential renal function (DRF) among refluxing ureters:

Grades of VUR (N)	DRF 20-30% No (%)	DRF>30-<45% No (%)
Grade II (37)	0 (0)	6 (16.21%)
Grade III (20)	4 (20)	5 (25)
Grade IV (18)	4 (22.22)	10 (55.55)
Grade V (10)	5 (60)	3 (30)
TOTAL (85)	15 (17.64)	24 (28.23)

<45% of DRF is considered abnormal. DRF of 20-30% was noticed in 15/85 (17.64%) children and 28.23% children had DRF of >30-<45%. Maximum number of children with Grade V VUR (50%) were found to have DRF of 20-30%, whereas DRF of >30-<45% was noticed in 55.55% of children with Grade IV VUR.

Table 6: Different grades of VUR on each side among children having bilateral VUR:

Grades of VUR	Males		Females	
	Right	Left	Right	Left
Grade II	9	7	7	6
Grade III	4	5	3	4
Grade IV	2	3	2	2
Grade V	2	2	1	1
	17	17	13	13

Out of 60 bilateral refluxing ureters, males accounted for 17 (34 VUR) and females being 13 (26 VUR). Among the 17 male children, 4 children (23.52%) had different grades of VUR on either side compared to 15.38% (2 out of 13) in females.

Discussion

The first attack of urinary tract infection can occur in the first year of life causing permanent parenchymal scarring in young vulnerable growing kidneys [9]. Distal ureteral courses obliquely through the bladder wall to the ureteral orifice. As the bladder wall distends with urine increasing compression of intramural and submucosal segment of ureter prevents retrograde flow of urine into distal ureter. But a shorter intramural-submucosal segment (normal ranging from 7-12 mm) increases the likelihood of VUR [10].

VUR due to UTI is the result of acute inflammatory reaction secondary to bacterial infection of renal parenchyma. The inflammation is mediated by cytokines released, resulting in focal parenchymal ischaemia and ultimately scarring.

Extent of renal damage after UTI depends on bacterial and host factors that mediate the response to infection. With energetic appropriate treatment, infection and inflammation is controlled, thereby decreasing/ preventing incidence of VUR [11]. VUR occurs unilaterally or bilaterally depending on urodynamics, severity of infections and early initiation of therapies [8].

Number of cases studied:

In the present study, 403 cases of UTI were followed up with male: female ratio of 1.22:1. Similar studies were done by others, but they studied only 30 children. Majority (66.99%) and male children (59.63%) were in the age group of 1-36 months.

Prevalence of VUR according to age and gender:

55 out of 403 (13.64%) found to have VUR with slight male predominance with M:F of 1.11:1. However, Al Ibrahim AAI and others observed 34 out of 82 (41.436%) of UTI with female predominance of 4.14:1. Similar high prevalence (36.84%- 39%) was also seen by others [12], [13]. 74.54% (41 out of 55) were in the age group of 1-36 months. 82.75% male children (24 of 29) and 65.38% of females (17 of 26) with VUR were also in this age group. Similar observations were noted by others [1,5].

Prevalence of various grades of VUR according to gender:

There were 85 refluxing ureters Grade II VUR (37 of 85) was noticed maximally (43.52%) and that to among males (23 of 37 - 62.16%). Similar observation was made by few [1,14] but others [15] noticed Grade IV VUR maximally.

Prevalence of Unilateral and Bilateral VUR:

Out of 85 refluxing ureters VUR was seen bilaterally in 30 out of 55 children (60 refluxing ureters) whereas unilateral VUR in 25 children. Such observation was not noticed by others.

Different grades of VUR in each side among children with bilateral VUR:

Out of 60 bilateral refluxing ureters seen in 30 children (17 male and 13 female), 4 out of 17 male (23.52%) and 2 out of 13 female children (15.38%) had different grades of VUR on either side. This was not noticed by others.

Differential renal functions among children with VUR:

Less than 45% of renal function on either side was considered abnormal. 45.88% (39 of 85) had DRF of <45%. 28.58% had DRF of >30-<45% and maximally with Grade IV (14 of 18) and Grade V (8 of 10) VUR respectively (77.77% and 80%). Similar observations were made by others [14], however they did not differentiate renal functions in different grades of VUR.

Table 7: Comparison of various grades of VUR:

Grade of VUR	HASHEM	Alia Abdulrahim	Present study
	Mahmoodzadeh ¹	Al-Ibrahim ¹⁴	(N=403)
	(N=135)	(N=82)	n (%)
	n (%)	n (%)	
Grade I	0	5(14.72)	0
Grade II	38(46.34)	13(38.23)	37(43.5)
Grade III	35(42.68)	8(23.52)	20(23.52)
Grade IV	8(9.77)	6(17.64)	18(21.17)
Grade V	1(1.21)	2(5.88)	10(11.76)
TOTAL	82(60.744)	34(41.46)	85(21.09)

Out of 85 refluxing ureters, 26 (30.58%) developed renal scars. Early energetic treatment in cases (41.17%) of VUR can avert formation of scars comparable with others [14].

Table 8: Comparison of renal scars in all grades of VUR:

Grade of VUR	Alia Abdulrahim Al-Ibrahim ¹⁴	Present study
	(N=34)	(N=85)
	n (%)	n (%)
Grade I	2/7 (28.57)	0
Grade II	2/13 (15.38)	5/37 (13.51)
Grade III	3/8 (37.50)	5/20 (25)

Grade IV	5/6 (83.33)	8/18 (44.44)
Grade V	2/2 (100)	8/10 (80)
TOTAL	14 (41.17)	26 (30.58)

In both the studies, high prevalence of renal scars was noticed in Grade V VUR.

Conclusion

To conclude, children less than 3 years of age are at higher risk of VUR after UTI, hence test like USG Abdomen, MCUG, DMSA should be done once the infection is controlled. Older children with UTI should undergo DMSA scan. Understanding the prevalence pattern, detection of early signs of disease and complications is crucial in administering appropriate treatment to minimise complications. This will further aid in providing appropriate management in cases of VUR according to severity.

References

1. Mahmoodzadeh H, Nikibakhsh AA, Karamyyar M, Gheibi S, Gholizadeh Hooshmand HR. Idiopathic hypercalciuria in children with vesico ureteral reflux and recurrent urinary tract infection. Urology journal. 2010;7(2):95-8.
2. Blumenthal | Vesicoureteric reflux and urinary tract infection in children Postgraduate Medical Journal 2006;82:31-35.
3. Fallahzadeh, M., Ghane, F., Hashemi, G., Derakhshan, A. Primary Vesicoureteral Reflux in Children in Southern Iran. Iranian Journal of Medical Sciences, 2015; 27(3) 110-113.
4. B. Manohar, T. Jayachandra Naidu, M. N. J. Sushma, B. Sasi Kumar, K. Sivaramudu, V. S. Anjan Kumar, L. Sividya. "Clinical Profile and Outcome of Urinary Tract Infections in Children Aged 1-12 Years". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 18, May 04, 2015; Page: 2666-2674.
5. Al-Ibrahim AA, Girdharilal RD, Jalal MA, Alghamdy AH, Ghazal YK. Urinary tract infection and vesicoureteral reflux in Saudi children. Saudi Journal of Kidney Diseases and Transplantation. 2002 Jan 1;13(1):24.
6. Snodgrass WT, Shah A, Yang M, Kwon J, Villanueva C, Traylor J, Pritzker K, Nakonezny PA, Haley RW, Bush NC. Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: a cross-sectional observational study of 565 consecutive patients. Journal of pediatric urology. 2013 Dec 1;9(6):856-63.
7. Stefanidis CJ, Siomou E. Imaging strategies for vesicoureteral reflux diagnosis. Pediatric Nephrology. 2007 Jul 1;22(7):937-47.
8. Piepsz A, Colarinha P, Gordon, Hahn K, Olivier P, Roca, Velzen JV, Sixt R. 8. Guidelines on 99m Tc-DMSA scintigraphy in children. Nuklearmedizin. 2000;23(4):311-6.

9. Salih QM, Yahya NB, Hussein NR. The Relationship Between Vesicoureteral Reflux and Recurrent Urinary Tract Infection in Children in Kurdistan Region, Iraq. *International Journal of Infection*. 2018 Apr;5(2).
10. Lim R. Vesicoureteral reflux and urinary tract infection: evolving practices and current controversies in pediatric imaging. *American Journal of Roentgenology*. 2009 May;192(5):1197-208. 10.
11. Garcia-Roig ML, Kirsch AJ. Urinary tract infection in the setting of vesicoureteral reflux. *F1000 Research*. 2016;5.
12. Honkinen OL, Ruuskanen OL, Rikalainen HE, Mäkinen EO, Välimäki IL. Ultrasonography as a screening procedure in children with urinary tract infection. *Pediatric infectious disease*. 1986;5(6):633-5.
13. Hoberman A, Charron M, Hickey Rw, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *New England Journal of Medicine*. 2003 Jan 16;348(3):195-202.
14. Sadeghi-Bojd S, Hashemi M. Hypercalciuria and recurrent urinary tract infections among children in Zahedan, Iran. *JPMMA*. 2008;58(624).
15. Ali ET, Alfaki EM, Abdelraheem MB. Primary vesicoureteral reflux in Sudanese children. *Saudi Journal of Kidney Diseases and Transplantation*. 15. 2014 Jul 1; (4):900.