

Vesicoureteric reflux in children

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Abstract

Aim: This study aimed to identify the differences between primary and secondary vesicoureteric reflux (VUR) and the effect of associated bladder abnormalities on kidney function.

Patients and Methods: We retrospectively reviewed the medical records of children with VUR who were followed up at King Abdulaziz University Hospital from January 2005 to December 2010. The review included results of radiological investigations and kidney function tests. We used Chi-square test for statistical analysis and paired *t*-test to compare group means for initial and last creatinine levels.

Results: Ninety-nine children were included in this study. Twenty (20.2%) had primary VUR, 11 had high-grade VUR, while 9 had low-grade reflux. All children with low-grade VUR had normal dimercaptosuccinic acid (DMSA). Renal scars were present in 72% of the children with high-grade VUR. The mean creatinine levels (initial and last) for both groups were normal. Seventy-nine (79.8%) children had secondary VUR, which was due to posterior urethral valves (PUV) (46.8%), neurogenic bladder caused by meningomyelocele (25.3%), non-neurogenic neurogenic bladder (NNB) (21.5%), or neurogenic bladder associated with prune belly syndrome (6.3%). Children with NNB, meningomyelocele and PUV had high creatinine at presentation with no considerable worsening of their kidney functions during the last visit. Renal scars were present in 49.4% of the children with secondary VUR.

Conclusion: Children with primary VUR and normal bladder had good-functioning kidneys, while those with secondary VUR associated with abnormal bladder caused by NNB, spina bifida or PUV had abnormal kidney functions. DMSA scans were useful in predicting higher grades of VUR in children with primary reflux.

Key Words: Children, neurogenic bladder, primary reflux, posterior urethral valves, secondary reflux, vesicoureteric reflux

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INTRODUCTION

Vesicoureteric reflux (VUR) is a congenital urinary tract defect caused by the failure of the ureter to insert correctly into the bladder. It occurs in up to 1% of the general population and is associated with recurrent urinary tract infections and

reflux nephropathy.^[1] Primary VUR is usually diagnosed following urinary tract infection (UTI) in children.^[2] However, secondary VUR occurs with obstructive uropathy such as posterior urethral valves (PUV)^[3] or neurogenic bladder caused by spinal lesion^[4] or non-neurogenic neurogenic bladder (NNB).^[5] The gold standard for diagnosing VUR is by voiding cystourethrogram (VCUG). However, recently dimercaptosuccinic acid (DMSA) scan was recommended to replace micturating cystourethrogram (MCUG) in detecting significant renal lesions in children with VUR.^[6] A normal DMSA scan of both kidneys [Figure 1] is associated with early resolution of VUR in infants and normal bladder function in the majority of the cases, while abnormal scans [Figure 2] are associated with severe VUR and abnormal bladder

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function.^[7] Therefore, abnormal renal scans are an important independent predictor of early failure to resolve VUR,^[7] while normal DMSA scans make VCUG unnecessary in the primary examination of infants with UTI.^[8]

In this study, we report our single-center experience with VUR. Our aim was to identify the differences between primary and secondary VUR and to investigate the effect of associated bladder abnormalities on kidney function. We also analyze all the radiological investigations to find out if DMSA scans could be used to replace VCUG as a first line investigation after ultrasound in children with UTI.

MATERIALS AND METHODS

We performed a retrospective chart review of all children with VUR who were followed up at the Pediatric Nephrology Clinic of King Abdulaziz University Hospital between January 2005 and December 2010. Ethical approval for the study was granted by the Biomedical Ethics Research Committee of King Abdulaziz University.

All children with VUR diagnosed with the use of VCUG were included in the study. They were graded according to the

international classification of VUR.^[9] For all patients included in this study, we collected demographic data including the age at referral, gender and nationality. We recorded the results of initial kidney function tests (serum creatinine) as well as the latest serum creatinine levels and the duration of follow up. All radiological investigations were also documented. These included renal ultrasound (US), MCUG and nuclear studies (DMSA scan and diethylenetriamine-pentacetic acid [DTPA] scan).

Primary VUR was defined as absence of evidence of neurogenic bladder and absence of PUV.^[2] Hydronephrosis was graded into mild, moderate and severe according to the degree of pelvicalyceal dilatation. We looked at the frequency of UTI and the type of organisms isolated. Frequent UTI was defined as three episodes or more per year.

Children with signs of neurogenic bladder on US examination, such as significant residual urine or thickened bladder wall or on MCUG, such as large bladder (megacystis) or massive VUR with abnormal bladder wall and no evidence of urethral obstruction were diagnosed as NNB or Hinman's syndrome.^[10] They were referred for urodynamic studies and had MRI of the spine to exclude spinal lesion as the cause of neurogenic bladder as per our unit protocol.

Statistical analysis: We analyzed the data to investigate the correlation between the grades of primary VUR and the presence of renal scars on DMSA scans. We used Chi-square test for statistical analysis and paired *t*-test to compare group means for initial and latest creatinine levels. Results were expressed as means (standard deviation). $P < 0.05$ was considered statistically significant.

RESULTS

Ninety-nine children were diagnosed as cases of VUR by VCUG. Seventy were boys and 29 were girls. Their age (SD) at referral was 2.8 (3.9) years. Their mean (SD) age at the time of the study was 6.7 (5.0) years. Mean (SD) duration of follow



Figure 1: Normal dimercaptosuccinic acid scan

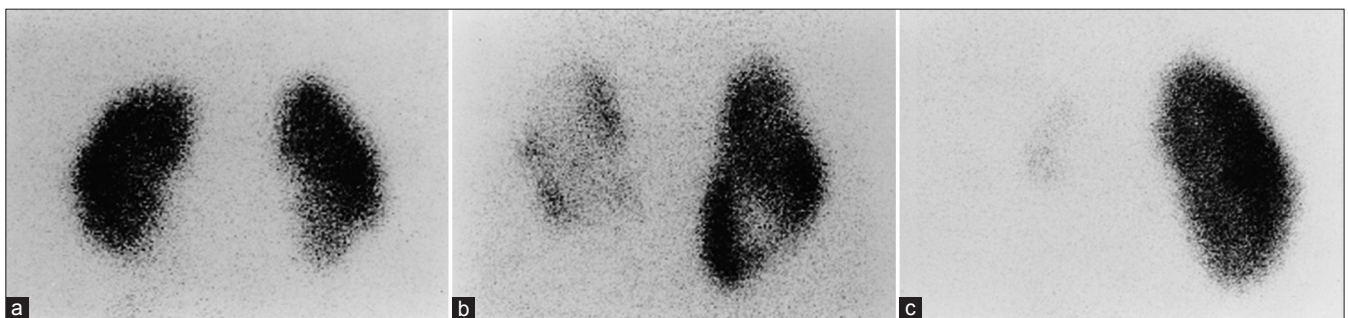


Figure 2: Examples of the renal scarring scoring system. (a) Normal left kidney, grade 1 scarring (lower pole of the right kidney). (b) Grade 2 (right kidney) and grade 3 (left kidney) scarring. (c) Grade 4 scarring (left kidney). Image adopted from Howard *et al.*^[18]

up was 3.5 (2.6) years. Fifty children were Saudis and the rest were of various nationalities.

Twenty children (20.2%) had primary VUR, which was investigated after an episode of UTI, while 79 (79.8%) had secondary VUR. Table 1 gives a summary of the details of children with primary and secondary VUR.

Among the children with primary VUR, 11 had high-grade reflux (grade IV or V), while 9 had low-grade reflux (grades I, II or III). Table 2 summarizes the differences among the children with respect to the grade of primary VUR.

When we classified hydronephrosis into mild, moderate and severe, the majority of children with low-grade VUR had a normal US, while 10 children (91%) with high-grade VUR had hydronephrosis. The mean (SD) serum at presentation for

the group with primary VUR was 54.4 (13.4) $\mu\text{mol/L}$ and the mean (SD) level at the last visit was 63.85 (15.8) $\mu\text{mol/L}$ ($P = 0.423$). There was no difference between the two groups in the levels of serum creatinine [Table 1]; however, children with low-grade VUR had less frequent UTI compared with children who had high-grade VUR ($P = 0.02$).

Vesicoureteric reflux was secondary to PUV in 37 children (46.8%), neurogenic bladder caused by meningomyelocele (MMC) in 20 children (25.3%), NNB in 17 children (21.5%), and neurogenic bladder associated with prune belly syndrome in 5 children (6.3%). Thirteen children with PUV had a picture of neurogenic bladder on MCUG.

Vesicoureteric reflux was secondary to neurogenic bladder in 42 children (53.2%). Twenty children had meningomyelocele. Their mean (SD) age at presentation to our unit was 4.3 (3.7) years. The mean duration of follow up was 5.0 (2.8) years. Eleven were girls and 9 were boys. Only four had normal US at presentation; 14 children had hydronephrosis, one had cystic changes and in one child the kidney was absent. Sixteen children had renal scars on their first DMSA scan. Their mean creatinine levels were 94.4 (77) $\mu\text{mol/L}$ and 153.6 (218.9) $\mu\text{mol/L}$ at presentation and at the last visit, respectively ($P = 0.244$ using paired T test).

In the children with VUR secondary to non-neurogenic neurogenic bladder ($n = 17$; 21.5%), 13 children presented with a history of UTI and impaired kidney function. They were found to have bilateral VUR and evidence of neurogenic bladder in the absence of spinal cord lesion. Their mean (SD) age at presentation was 4.3 (4.1) years. The mean (SD) duration of follow up was 9 (4) years. Ten of them had hydronephrosis and hydronephrosis on US examination, while 11 had thickened bladder. Their mean creatinine at presentation was 196 (110) $\mu\text{mol/L}$ and at the last visit it was 254 (106) $\mu\text{mol/L}$. All the patients had a normal spine on magnetic resonance imaging (MRI). Dimercaptosuccinic acid scan showed renal scars in seven children; the scars were bilateral in two of the patients.

Posterior urethral valves and vesicoureteric reflux: Thirty-seven children were referred to the clinic at the mean age of 2.4 (3.8) years, and the mean (SD) duration of follow up was 2.8 (2.2) years. Their mean age at the time of the study was 5.5 (4.8) years. Ultrasound examination revealed that 36 children had bilateral hydronephrosis, 30 had bilateral hydronephrosis, 4 had unilateral hydronephrosis, and 20 had thickened trabeculated bladder. Sixteen children had renal scars on DMSA, while 21 children had none. Their mean creatinine at first presentation was 208.6 (245.75) $\mu\text{mol/L}$, and at the last visit, there was a non-significant increase of the creatinine levels to 208.6 (245.75) $\mu\text{mol/L}$ ($P = 0.24$).

Table 1: Comparison of the characteristics in the children with primary and secondary vesicoureteric reflux*

	Primary VUR	Secondary VUR
Frequency (percent)	20 (20.2)	79 (79.8)
Gender (female:male)	11: 9	18: 61
Age at diagnosis (years)	1.8 (1.8)	MMC: 4.3 (3.7) NNB: 4.3 (4.1) PUV: 2.4 (3.8)
Duration of follow up (years)	3.4 (2.9)	5.2 (4.9)
Creatinine at presentation ($\mu\text{mol/L}$)	54.4 (13.4)	MMC: 94.4 (77) NNB: 196 (110) PUV: 208.6 (245.75)
Creatinine at last visit ($\mu\text{mol/L}$)	63.85 (15.8)	MMC: 153.6 (218.9) NNB: 254 (106) PUV: 192.97 (160.7)
DMSA scan	Lower grade: Normal Higher grades: 80% scars	MMC: 80% scars NNB: 54% scars PUV: 49%

DMSA: Dimercaptosuccinic acid, MMC: Meningomyelocele, NNB: Non-neurogenic neurogenic bladder, VUR: Vesicoureteric reflux. *Data are presented as mean (SD) unless otherwise indicated

Table 2: Differences among the children with respect to the grades of primary vesicoureteric reflux*

	Vesicoureteric grade		P value
	Grades I, II, and III (n=9)	Grades IV and V (n=11)	
US finding			
Normal (percent)	8 (88.9)	1 (9.1)	<0.001
Hydronephrosis (percent)	1 (11.1)	10 (90.9)	
DMSA scan			
Normal (percent)	9 (100.0)	3 (27.3)	<0.001
Scars (percent)	0 (0.0)	8 (72.7)	
Mean (SD) creatinine at presentation ($\mu\text{mol/L}$)	43 (20.9)	59.21 (70.9)	Not significant
Mean (SD) creatinine at last visit ($\mu\text{mol/L}$)	39.5 (13.1)	74.29 (82.9)	Not significant
Frequency (percent) of UTI	1 (11.1)	7 (63.6)	0.02

DMSA: Dimercaptosuccinic acid, US: Ultrasound, UTI: Urinary tract infection. *Data are presented as frequency (percent) and mean (SD) unless otherwise indicated

Among the children with secondary VUR, renal scars were identified on DMSA scans in 39 of the cases (49.4%).

DISCUSSION

In this study, we highlight different types of bladder dysfunction that are associated with VUR. Only 20 children (20.2%) had primary VUR diagnosed after investigations, following an episode of UTI. Ultrasound and DMSA scans were useful tools in predicting the grades of VUR in the patients. All children with low-grade VUR had normal DMSA scans, and the majority of the cases had normal US, while the majority of children with high-grade VUR had hydronephrosis on US examination and scarred kidneys on DMSA scans. This is in agreement with the recommendation that a normal DMSA scan makes VCUG unnecessary in the primary examination of infants with UTI.^[8] In a similar report on children who suffered their first febrile UTI, Lee *et al.* reported that most high-grade VUR could be detected by US and DMSA scans, with a combined detection rate of 95.3%. Furthermore, their findings suggested that spontaneous improvement without complications was expected in patients with either low or high grade VUR and normal US and DMSA scan.^[11]

In the current study, children with high-grade VUR had a significantly higher frequency of UTI, and this had an impact on the size of renal lesions after an episode of pyelonephritis. Dias *et al.* from Brazil reported severe grade of VUR as a risk factor for recurrent UTI.^[12] In general, children with grade III or IV reflux are more likely to have larger renal scars. On the other hand, acute lesions of important size may develop even in the absence of VUR.^[13]

All the children in this study who had normal bladder appearance on VCUG had normal kidney function in both cases of low- and high-grade VUR. Thirteen children had neurogenic bladder with bilateral VUR with no evidence of spinal lesion and were therefore labeled as NNB. There was significant delay in referring these patients to our clinic as they had considerable renal impairment. The presence of an abnormal bladder was a prediction for abnormal kidney function and progressive worsening of kidney function. Non-neurogenic bladder dysfunction and vesicoureteral reflux in children could be caused by bladder disturbances such as detrusor instability (overactive bladder) and bladder sphincter dyssynergia (dysfunctional voiding).^[5,13] Similar to our observation, Avlan *et al.* from Turkey reported that overactive bladder plus dysfunctional voiding are major risk factors for VUR, UTI and renal damage.^[14] The appropriate treatment of VUR in this group of patients depends on treating the elimination syndrome by regular evacuation of the bladder by clean intermittent catheterization or diversion.^[13]

Vesicoureteric reflux was caused by neurogenic bladder associated with spina bifida in 20 children. Spina bifida is still an important cause of end-stage renal failure (ESRF) in developing countries,^[4,15] and there is usually a considerable delay in referring affected children to start bladder management as was the case in our cohort. Our recommendation for all children with neurogenic bladder is to do clean intermittent catheterization and to put them on prophylactic antibiotics.

Posterior urethral valves were the underlying cause of VUR in about one-third of our cohort. There was also a considerable delay in the referral of the children to a tertiary unit, and they had significant renal impairment by the time they were diagnosed with this anomaly. Delayed presentation of PUV is usually associated with poor prognosis and rapid progression to ESRF.^[16] Abnormal bladder, observed in the majority of children in this study, has also been reported a factor of poor prognosis in children with PUV.^[17]

Our study was limited because of the less number of children with primary VUR. However, it emphasizes the importance of looking at bladder abnormalities in children with VUR and the need for early referral, particularly in children with secondary VUR.

CONCLUSION

Children with primary VUR and normal bladder had a good prognosis with a normal kidney function, while children with secondary VUR associated with abnormal bladder caused by NNB, spina bifida or PUV had abnormal kidney functions. DMSA scans were useful in predicting higher grades of VUR in children with primary reflux.

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