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Outcome of Primary Vesicoureteric Reflux (VUR): A Cohort Study in Chinese Children

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Abstract

Background: Primary vesicoureteric reflux (VUR) is a common in children but data on its natural course are scanty in the Chinese population. ***Objective:*** To delineate the characteristics and evaluate the natural course of Chinese children with VUR. ***Method:*** Chinese children diagnosed to have VUR in a regional hospital, between 1/1/1996 and 31/12/2000, were recruited. Their characteristics at initial presentation and clinical outcome at 5-year old were studied. ***Results:*** Sixty-three Chinese children with primary VUR were recruited. The median age at presentation was 8 months old. Seventy-nine percent of patient presented as urinary tract infection (UTI). A male predominance (65% of patient) was noted and both ureters were equally affected. Among the 103 refluxing renal units, 18.5% were grade I, 23.3% grade II, 33.0% grade III, 14.5% grade IV and 10.7% grade V. Of 42 patients with 65 refluxing units who had repeat micturiting cystourethrogram (MCUG) at 5 years old, 48% had resolved. The rates of resolution were 73% for grades I/II, 31% for grades III/IV, and zero for grade V VUR. For those who had undergone 2,3-dimercaptosuccinic acid (DMSA) scans at presentation, 39% showed different degrees of renal scarring. At last assessment none of our patients had developed hypertension. One patient had stage IV chronic kidney disease and one patient had significant proteinuria. ***Conclusion:*** Unlike Caucasians, Chinese children have a lower prevalence of VUR and almost half of our studied patients showed resolution of VUR at 5 years old.

Key words Chinese; Prognosis; Vesicoureteric reflux

Introduction

Vesicoureteric reflux (VUR) is a common abnormality affecting about one-third of children who presented with urinary tract infection (UTI) at young age. Among them one-third would have resulted in renal scarring. Other co-morbidities like hypertension, reflux nephropathy and renal failure are well known.[1] Current management of VUR is based on the fact that most of them would resolve spontaneously with time. Therefore, antibiotic prophylaxis is used with an aim to reduce symptomatic UTI and subsequent renal scarring before complete resolution occurs.

Better knowledge on the prevalence, natural course and outcome of VUR would help us in daily clinical management and counselling. This information is well known in Caucasian population.[1] Data for the American Blacks are also available.[2] However, there were only a few studies on the Chinese population and most of them are of small sample size.[3-5] Therefore, we conducted a retrospective cohort study aiming at evaluating the characteristics, natural course and outcome of Chinese children with primary VUR.

Methods

Clinical data of children who attended a regional tertiary hospital with the diagnosis of VUR between 1/1/1996 to 31/12/2000 were reviewed. VUR was diagnosed by

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micturiting cystourethrogram (MCUG) on investigation of children with first symptomatic UTI or hydronephrosis.

Children who were diagnosed to have VUR were put on antibiotic prophylaxis irrespective of the grading of VUR until reassessment at 5 years old with MCUG and DMSA scan. Their clinical conditions, compliance to antibiotics prophylaxis, frequency of UTI, blood pressure and urine analysis were monitored at each clinic visit. Renal function test and radiological imaging were done when needed. DMSA scan was the method for assessing the degree of renal scarring. It was done in all VUR patients and was repeated at 5 years old if indicated. Imaging that was performed within 3 to 6 months after an UTI episode was repeated 6 months later to avoid false-positive result caused by post-inflammatory changes.[6,7] If VUR persists after 5-year old, the child would be referred to paediatric urologist for counselling on various options of treatment. Indications for surgery before 5 years old include abnormal renal function, recurrent UTI despite antibiotic prophylaxis, progressive renal scarring on follow-up DMSA scan and poor renal growth on ultrasound (USG) evaluation.

Definitions

Vesicoureteric reflux (VUR) was defined as retrograde flow of urine from bladder to the upper urinary tract. All VUR were diagnosed by direct voiding micturiting cystourethrogram (MCUG). The severity of the refluxing units was graded by the International Study Classification (International Reflux Study in Children Writing Committee).[8] Grade I indicated VUR up to ureter only. Grade II indicated reflux up to ureter and pelvis with no dilatation. Grade III indicated reflux up to renal pelvis with mild dilatation; slight ureteral tortuosity and slightly blunting of fornices might be seen. Grade IV indicated that there was moderate dilatation of the ureter, renal pelvis & calyces; sharp angle of fornices would be completely obliterated but papillary impressions would be preserved. Grade V indicated that there was grossly dilated ureter and pelvis; marked tortuosity of ureter and calyceal clubbing would also be present. *Primary VUR* referred to congenital abnormality of the vesicoureteric junction without any urinary tract abnormality that might result in reflux. *Secondary VUR* referred to those results from bladder dysfunction or urinary tract abnormality.

Renal scarring was divided into 4 types according to the DMSA scan findings. Type 1: Mild scaring indicated that there were no more than 2 scarred areas. Type 2: Moderate scarring indicated that there were more than 2 renal scars with some areas of normal parenchyma in-between. Type 3: Severe scarring indicated that there was contraction of the whole kidney with or without very few scars in the outline. Type 4 renal scarring indicated that the kidney had little or no uptake of DMSA and had less than 10% of the overall function.[9]

Hypertension was defined as an average systolic or diastolic blood pressure higher than 95th percentiles for age, gender and height on ≥3 occasions. Stage I hypertension was defined as blood pressure at 95-99th percentile plus 5 mmHg and stage II hypertension is defined as blood pressure >99th percentile plus 5 mmHg.[10]

Proteinuria was defined as urine protein excretion of greater than 4 mg/m^2/hr calculated from a 24-hour urine sample.

Chronic kidney disease (CKD) was divided into 5 stages according to National Kidney Foundation (K/DOQI) guideline. Stage I was GFR ≥90 ml/min/1.73m^2 (normal). Stage II was GFR 60-89 ml/min/1.73m^2, stage III was 30-59 ml/min/1.73m^2, stage IV was 15-29 ml/min/1.73m^2 and stage V was <15 ml/min/1.73m^2.[11]

Glomerular filtration rate (GFR) was estimated by Schwartz equation i.e.

$$\text{GFR (ml/min/1.73m}^2) = \kappa \times \text{Body height (cm)} / \text{Plasma creatinine (umol/L)}$$

Where $\kappa = 49$, for girls 2-16 years and boys 2-13 years, $\kappa = 62$ for boys of 13-16 years.[12]

Results

Seventy-five Chinese children were diagnosed to have VUR during the study period. Among them 65 suffered from primary VUR and 10 were secondary to bladder dysfunction. Two patients were excluded due to incomplete data available. Therefore 63 patients were eligible for the study.

Among the 63 patients recruited, 41 (65%) were male and 22 (35%) were female. Their mean age at presentation was 17±21 months old, ranging from 1 to 94 months and the median was 8 months old. The duration of follow up ranged from 1 to 143 months with the mean of 77±34 months (Table 1). Fifty patients (79%) presented as UTI and 2 patients (3%) presented as antenatal hydronephrosis. In the remaining eleven patients (18%), VUR was detected incidentally. MCUG was performed in this group of patients because of hydronephrosis, which was detected during abdominal ultrasound examination for single umbilical

Table 1 Demographic data of Chinese children with primary VUR

Characteristics	Number of patients (%)
Sex	
Male	41 (65)
Female	22 (35)
Laterality	
Unilateral	28 (44)
Bilateral	35 (56)
Age at presentation	
Mean±SD	17±21 months old
Median	8 months old
Range	1 to 94 months old
Duration of follow up	
Mean±SD	77±34 months old
Median	78 months
Range	1 to 143 months

artery (2 patients), ear abnormalities (2 patients) multiple congenital abnormalities (3 patients), work up for hepatosplenomegaly (3 patients) and impaired renal function in a premature baby. The number of children aged 0-5 years old, diagnosed to have UTI in our hospital in the same study period was 379 patients. Among these 379 patients, only 214 patients underwent MCUG examination. Hence, the incidence of primary VUR in children presenting as UTI at the age of 0-5 years old was estimated to be 23.3% (50 patients in 214 patients). This coincided with the low incidence of VUR reported from previous studies from Chinese children. Among those presenting as UTI, 3 patients had renal insufficiency of various degrees at presentation. One patient had acute renal failure with septic shock at presentation and required haemofiltration as acute renal replacement therapy.

Twenty-eight patients (44%) had unilateral VUR, and 35 patients (56%) had bilateral VUR. Left (52.4%) and right (47.6%) ureters were equally affected. Five patients had unilateral duplex urinary system, 2 patients had unilateral renal agenesis and 1 patient had single kidney due to unilateral nephrectomy for fibrosarcoma. These made up a total of 103 refluxing renal units for the study. Of all refluxing ureters, the majority was grade II (23.3%) or III (33.0%). Grade I VUR was found in 18.5% while grades IV and V occurred in 14.5% and 10.7% respectively (Table 2). Three patients refused DMSA examination leaving 99 refluxing units evaluated for associated renal scarring after first UTI. Thirty-nine refluxing units (39%) had detectable renal scarring at the time when VUR was first diagnosed (Table 3). Among those affected, 23 (59% of 39 refluxing units) had mild scarring, 4 (10.2%) had moderate scarring, 8 (20.5%) had severe scarring and 4 (10.3%) had contracted renal units.

At re-evaluation of VUR status in our cohort, 42 patients (65 refluxing renal units) had MCUG repeated at 5 years of age. Among the 21 patients who were excluded, 4 patients were near 5 years old at diagnosis therefore MCUG were not repeated. Four patients had anti-reflux surgery done before they were 5 years old. Bilateral high-grade VUR and recurrent UTI were the major indications for surgical intervention before 5 years of age (Table 4). Twelve patients

Table 2 Distribution of initial grading of VUR in the refluxing renal units

	Number of renal units (%)		
	Left	Right	Total
I	11 (10.7)	8 (7.8)	19 (18.5)
II	11 (10.7)	13 (12.6)	24 (23.3)
III	16 (15.5)	18 (17.5)	34 (33.0)
IV	9 (8.7)	6 (5.8)	15 (14.5)
V	7 (6.8)	4 (3.9)	11 (10.7)
Total	54 (52.4)	49 (47.6)	103 (100)

Table 3 Distribution of initial renal scarring in relation to the initial grading of VUR

		Number of renal units with scarring				
Initial grading of VUR	Normal DMSA (no scar)	Mild	Moderate	Severe	Contracted	Total
I	14	3	0	0	0	17
II	15	4	0	3	0	22
III	23	8	1	0	3	35
IV	6	4	2	1	1	14
V	2	4	1	4	0	11
Subtotal		*23*	*4*	*8*	*4*	
Total	60			39		99

had incomplete data and 1 patient was awaiting the 5-year old assessment. The spontaneous complete resolution rate at 5 years of age for grade I/II reflux was 73% & 31% for grade III/IV. None of the grade V VUR resolved at assessment at 5 years of age. Overall, 48% of patients showed spontaneous complete resolution, 32% showed improvement in VUR grading, but 20% showed no change or deterioration (Table 5).

For those 27 patients who were found to have renal scarring at initial presentation, 8 patients were followed-up for less than 5 years and 19 patients were included in the assessment of medium term outcome of renal function. Twelve of them were male and 7 were female. Their mean duration of follow up was 86.9±19.4 months, ranging from 63 to 120 months. None of our patients developed hypertension. One patient was in Stage IV chronic kidney disease with GFR 20.6 ml/min/1.73m^2 and proteinuria of 1.5 gm/day. Exclude this patient, the mean GFR was 119±27.6 ml/min/1.73m^2 (range 72 to 173 ml/min/1.73m^2). Another patient had significant proteinuria of 0.9 gm/day but with normal GFR and blood pressure (Table 6).

Discussion

Male Predominance

Our data showed a male predominance (with a male-to-female ratio of 2:1) in primary VUR in children with UTI, while those reported by Skoog & Belman[2] showed a female predominance in Whites and Blacks with a male-to-female ratio of 1:7 and 1:3 respectively. Previous studies in Chinese children also reported a male predominance or equal sex distribution.[3-5] Hence, a genuine ethnic difference might be present. How this gender difference predicts the outcome of VUR is, however, uncertain. Silva et al[13] reported a large cohort of 735 children. Variables including race, gender, age at diagnosis, clinical presentation, dysfunctional voiding and renal damage were analysed. Gender as an isolated variable was a poor predictor of clinical outcome in their unselected series of children with primary VUR. Boys were found to have more severe pattern at baseline, but girls had a greater risk of dysfunctional voiding and recurrent UTI during follow up.

Table 4 Characteristics of patients who required anti-reflux surgery before 5 years old

Sex	Age at presentation (months)	VUR grading	Renal scarring	Indication for surgery	Type of surgery done
M	16	Left: I Right: III	Left: mild Right: moderate	Frequent UTI	Bilateral re-implantation of ureters
M	5	Left: III Right: III	Left: contracted Right: 0	Frequent UTI	Bilateral re-implantation of ureters
M	10	Left: V Right: V	Left: severe Right: 0	Frequent UTI, ARI	Bilateral re-implantation of ureters
M	15	Left: V Right: V	Left: severe Right: severe	UTI, ARI requiring dialysis	Bilateral re-implantation of ureters

UTI: urinary tract infection; ARI: acute renal insufficiency

Table 5 Resolution or change in grades of VUR in 42 patients (with 65 refluxing renal units) at 5 years old

At 1st assessment (number of refluxing renal unit)		At assessment at 5 years old (number of refluxing renal unit)			
		VUR resolved	Grading improved	Grading static	Grading deteriorated
I	8	6 (75%)	0	1	1
II	21	15 (71%)	4	1	1
III	25	8 (32%)	12	5	0
IV	7	2 (29%)	2	3	0
V	4	0 (0%)	3	1	0
Total	65	31 (48%)	21 (32%)	11 (17%)	2 (3%)

Table 6 Characteristics and outcome of 19 patients with initial renal scarring and follow up for more than 5 years

Characteristics	Number of patients
Sex	
Male	12
Female	7
Initial VUR grading	
I	3
II	3
III	8
IV	7
V	6
Duration of follow up	
Mean	86.9±19.4 months
Median	80 months
Range	63-120 months
Outcome at last follow up	
Chronic Kidney Disease (CKD)	
Stage I	15
Stage II	3
Stage III	0
Stage IV	1
Stage V	0
Glomerular Filtration Rate (GFR) (exclude stage IV CKD)	
Mean	119±27.6 ml/min/1.73m^2
Range	72 -173 ml/min/1.73m^2
Hypertension	0
Significant Proteinuria	2

Early Identification of Asymptomatic VUR May Be Worthwhile

Majority (79%) of our patients presented as UTI. Among them, 3 (4.7%) had renal insufficiency at presentation. One patient with bilateral grade V VUR presented as acute renal failure requiring dialysis. His renal function continued to deteriorate after resolution of UTI. Two patients (each with bilateral grade IV & grade V VUR) presented with raised serum creatinine, which returned to near normal after treatment of the infection.

With the possibility of such devastating initial presentation, early identification of patients with asymptomatic VUR might be beneficial. Screening of asymptomatic siblings would be worth considering because it had been shown by Ataei et al[14] that 42.5% siblings of patients with VUR suffered from the same problem and 80.8% of them would be asymptomatic. However, renal scarring could be identified in most of them (66.6% of those with mild-to-moderate VUR and 100% of those with severe VUR). These results were comparable with that reported by the American Urological Association (AUA).[1] Similarly, screening for those with antenatal hydronephrosis might also allow early diagnosis, monitoring & treatment and thus, optimise the outcome.

Lower Prevalence of Primary VUR Among Chinese Children Who Were Investigated for First UTI

The prevalence of VUR in the general healthy population is unknown and is estimated to be 1-2% in Caucasians. Most VUR in children was detected while investigating the first febrile urinary tract infection. Prevalence of VUR among young children with UTI was 30-40% in Caucasians.[1] Our data showed that the prevalence of primary VUR detected from UTI in Chinese children (less than 5 years old) was 23%. This incidence coincides with the lower prevalence of 21.6% to 26% as reported by other local studies.[3-5,15] We however, have to take into consideration that only two-third of patients with UTI in our hospital underwent MCUG examination during the study period. The true prevalence of VUR in UTI may not be truly reflected. Yet, combining with other local studies, a true ethnic difference might be responsible for such difference. The variation in the diagnosis of UTI could also affect the incidence. Over-diagnosis of UTI could be a cause of underestimation of the prevalence. Clinical guidelines on diagnosis, investigation and treatment of UTI had been published by the local health authority in year 2002 hoping to advice paediatricians, family doctors and emergency room physicians in unifying the criteria for diagnosis.[16,17] This facilitates a better estimation of VUR prevalence in the local population.

Higher Resolution Rate in Low Grade VUR

The overall spontaneous complete resolution rate of our patients at 5 years old was 48%, which was slightly higher than 35% in Whites and 37% in Blacks.[2] When resolution rates of different grading were considered, it was found that the lower the grading, the higher the chance of resolution. At 5-year assessment, 73% of grade I/II VUR, 32% of grade III VUR and 29% of grade IV VUR resolved. None of the grade V resolved. For those unresolved VUR, 32% showed improvement in the grading. These data are important for counseling of patient on the choice of treatment. A recent report from Thailand[18] also showed a resolution of 72% in grade I-III VUR and 37% in grade IV-V which was very similar to our data. The International Vesicoureteric Reflux Study[19,20] reported a progressive reduction in severity of reflux during the first 5 years of follow up and it continued to improve up to 10 years. Over a 10 years period, 47% of

high grade reflux disappeared. Variables that had been suggested as predictors of VUR resolution included nonwhite race, mild grade VUR, absence of renal damage and absence of dysfunctional voiding.[21]

Renal Scarring at Presentation

The percentage of renal scarring at presentation was 39%, which was comparable with 20-40% quoted by AUA.[1] Other local study showed similar results.[22] At the end of our study, one patient developed chronic renal failure (the patient who developed acute renal failure & required dialysis at presentation), otherwise the outcome seemed to be favourable. This echoed our previous advice on early identification of patients with VUR because of the possible devastating outcome. Moreover, we must bear in mind that this favourable result only reflected the outcome of a 5-year follow up of those patient with reflux nephropathy (VUR with renal scarring) only. Silva et al[23] in their recent report estimated the probability of chronic kidney disease (GFR <75 ml/min per 1.73m^2) for patients with bilateral severe VUR to be 15% by 10 years after VUR diagnosis. Hence, more complications would be observed after a longer period of follow up. A less favourable long term outcome among those who had already had mild impairment in GFR or hyper-filtration during the study period would be expected.

Conclusion

The majority of children with vesicoureteric reflux presented as urinary tract infection. At 5-year old assessment, half would resolve spontaneously and one third would improve in grading or remain static. One third of the patients will have detectable renal scarring at presentation. Although the 5-year assessment of their renal function is satisfactory, their long-term outcome is still uncertain.

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