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High Spontaneous Resolution Rates of Severe Primary Vesicoureteral Reflux and Minimal Development of New Renal Scars

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Purpose: The previous reports regarding VUR resolution were not precise due to early frequent surgical intervention. We evaluated the spontaneous resolution (SR) rate and the incidence of new renal scars in primary VUR, focusing on severe reflux.
Methods: Medical records of 334 patients with primary VUR who were on medical prophylaxis without surgery for 1 to 9 years, were retrospectively reviewed. Medical prophylaxis was initiated with low-dose antibiotic prophylaxis or probiotics. Radioisotope cystourethrography was performed every 1 to 3 years until SR of reflux. New renal scar was evaluated with follow-up ^{99m}Tc DMSA renal scan.
Results: The SR rates decreased as VUR grades were getting higher (P=0.00). The overall and annual SR were 58.4% and 14.9%/yr in grade IV reflux and 37.5% and 9.3%/yr in grade V reflux. The median times of SR were 38 months in grade IV reflux and 66 months in grade V reflux. The probable SR rates in grade IV and V reflux were 7.8% and 8.9% in the 1st year, 46.0% and 30.8% in the 3rd year and 74.4% and 64.4% in the 5th year. The incidences of new renal scars between low to moderate reflux and severe reflux showed no significant difference (P=0.32).
Conclusion: The SR rates of severe primary VUR were higher than previously reported and most new renal scars were focal and mild.

Key words: Annual spontaneous resolution rate, Median time to SR, Medical prophylaxis

Introduction

Primary vesicoureteral reflux (VUR) is a common developmental anomaly that was thought to predispose to recurrent pyelonephritis, progressive renal scarring and end stage renal disease. This concept and the following published data led to active search and management of primary VUR and the guideline was published by American Urologic Association (AUA) in 1997[1,2]. According to the guideline, antibiotic prophylaxis has been the main treatment option under expectation of spontaneous resolution (SR) of VUR. However, surgical interventions have been frequently performed in moderate to severe reflux which were considered to have lower chance of SR and higher risk of progressive renal scarring[2,3]. However, a considerable number of moderate to severe reflux (Grade III, IV) eventually resolved after the long-term follow-up (10-15 years)[4-7]. And severe reflux (Grade IV, V) diagnosed in neonates and

infants also resolved spontaneously in high percentage (29-44%) during the first follow-up year[8-10]. Moreover, severe renal scars which we have concerned about were found to be congenital in origin rather than acquired[11,12]. The postnatally acquired renal scars in severe reflux were found to be mild[13]. So, the conventional guidelines for managing primary VUR were revised to less aggressive approach, and surveillance alone has become one of the management options in mild reflux[14-16]. Also, the protective effects of both antibiotic prophylaxis and surgical intervention on the development of severe renal scars have been continuously questioned[17-21]. In addition, the Cochrane review concluded that it was uncertain whether we could prevent severe renal scarring by treating primary VUR and concerned that we may treat too many to prevent a few and small acquired renal scars[22].

To prove whether severe primary VUR is not a serious condition as it was thought to be, more evidence is necessary to support it. Precise estimation of the SR rate and the incidence of new renal scar in severe reflux are very crucial. However, the previously reported SR rates were quite variable among studies and they might be mistakenly underestimated because of the short-term follow-up and the high rates of surgical interventions (14-46% in severe reflux)[1-6].

The purpose of this study was to evaluate the SR rate and the incidence of new renal scars in patients with primary VUR, who were on long-term medical prophylaxis without surgery as possible focusing on severe reflux.

Materials and methods

Medical records of patients (n=438) who were diagnosed as Primary VUR after UTI or antenatal hydronephrosis between 1998 and 2012 at Ewha Womans University Medical Center, were retrospectively reviewed. Since 1998, the management policy for primary VUR was to select medical prophylaxis as a first line therapy and continue until SR without surgery as possible. Surgical interventions were performed usually by parental preferences in 6.2% (n=22) with bilateral renal scars (n=9), frequent UTI (n=10) or persistent VUR (n=3). The patients (n=104) who went to surgery (n=22) and lost the follow-up (n=82) were excluded.

Among eligible 334 patients (229 boys and 105 girls, age 18.4 + 29.6 months, range 0-168 months) with primary VUR, 101 patients had severe reflux (77 in grade IV reflux, 24 in grade V reflux). The reflux grade in bilateral VUR was determined by the worst one. If antibiotic prophylaxis was initially selected, it was usually switched to probiotic prophylaxis after 1-3 years. Patients were regularly followed up every 1 to 3 months for urinalysis and urine culture until SR (1 to 9 years). Radioisotope cystourethrography was performed every 1 to 3 years until SR. Resolution of VUR was confirmed when there is no visible reflux in follow-up radioisotope cystourethrography. New renal scarring was evaluated with follow-up 99mTc DMSA renal scan at the time of SR of primary VUR.

To evaluate the SR rates, Kaplan-Meier survival curves were conducted using SPSS version 16.0 for Windows. The incidences of recurrent UTI and new renal scarring were analyzed by the chai-square statistics using SPSS version 16.0 for Windows. *P* values less than 0.05 were considered as statistically significant.

Results

1. The SR rate of primary VUR

Among 334 eligible patients with primary VUR, reflux resolved in 245 patients and persisted in 89 patients at the point of the study. Kaplan-Meier survival curves showed that the SR rates decreased as VUR grades were getting higher (*P*=0.00, Fig. 1). The survival curves in each reflux grade were all shifted to the left than the previous AUA report[2]. The overall and annual SR rates in severe reflux were 58.4% (45/77) and 14.9% per year in grade IV reflux and 37.5% (9/24) and 9.3% per year in grade V reflux, which were lower than those of low grade reflux. The median times of SR in severe reflux were 38 months in grade IV reflux and 66 months in grade V reflux (Table 1).

The probable SR rates in grade IV and V reflux, based on Kaplan-Meier survival curves, were 7.8% and 8.9% in the 1st year, 27.2% and 13.5% in the 2nd year, 46.0% and 30.8% in the 3rd year, 57.4% and 46.6% in the 4th year and 74.4% and 64.4% in the 5th year (Fig. 1, Table 2) which were higher than expected. These results showed that a substantial number of severe reflux, which was known to have little chance of SR, resolved spontaneously after the long-term follow-up

to question the effect of surgical intervention.

2. Development of new renal scars until SR

The incidence of new renal scars in grade I was negligible (0%, 0/12). They were 8.1% in grade II reflux (3/37), 10.0% in grade III reflux, 10.5% (6/57) in grade IV reflux and 18.2 % (4/22) in grade V reflux. The incidences of new renal scar development between low to moderate grade VUR (I-III) and severe grade VUR (IV-V) showed no significant difference (P=0.32, Table 3). All new renal scars were focal and mild.

Table 1. The Overall and Annual Spontaneous Resolution (SR) Rates and Median Times to SR according to Reflux Grades

VUR	No.	Overall SR No. (%)	Annual SR %/yr	Median time to SR, months
Grade I	35	32 (91.4)	45.0	12
II	93	73 (78.5)	22.7	15
III	105	86 (81.9)	17.0	23
IV	77	45 (58.4)	14.9	38
V	24	9 (37.5)	9.3	66

Abbreviation: VUR, vesicoureteral reflux.

Table 2. The Probable Spontaneous Resolution (SR) Rates of Primary Vesicoureteral Reflux (VUR) for 5 Years Based on Kaplan-Meier Curve

VUR Grade	Probable SR				
	1st yr	2nd yr	3rd yr	4th yr	5th yr
I	34.3	89.3	92.9	92.9	92.9
II	22.6	66.7	74.5	89.8	94.9
III	32.4	51.5	66.1	80.7	85.0
IV	7.8	27.2	46.0	57.4	74.4
V	8.9	13.5	30.8	46.6	64.4

Discussion

The first concern in severe primary VUR was little chance of SR. However in this study, the overall SR rates of severe reflux (58.4 and 37.5% in grade IV and V reflux), the annual SR rates (14.9% and 9.3% in grade IV and V reflux) and the

Table 3. The Incidence of New Renal Scar after Spontaneous Resolution of Primary Vesicoureteral Reflux (VUR)

VUR Grade	No. of patients	New renal scar No. (%)
I	12	0 (0)
II	37	3 (8.1)
III	60	6 (10.0)
IV	57	6 (10.5)
V	22	4 (18.2)

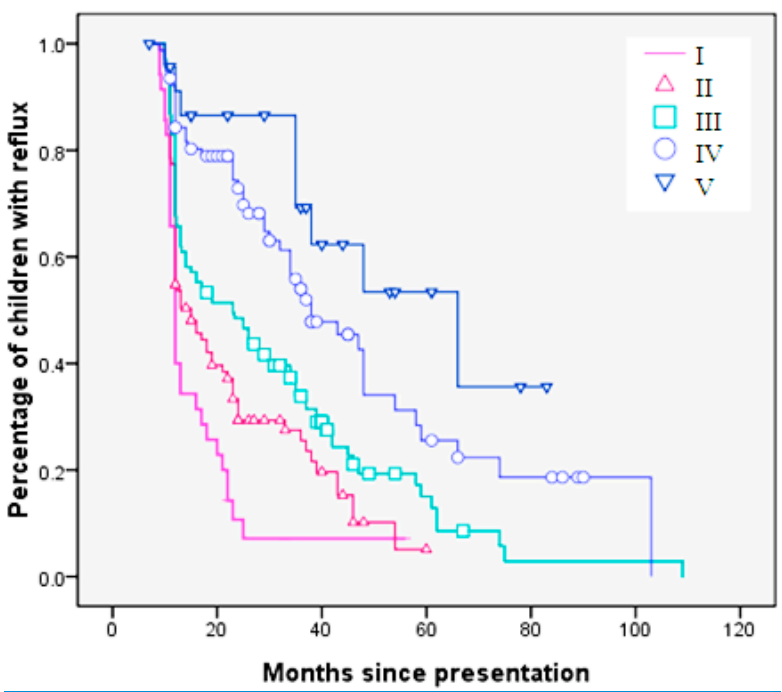

Fig. 1. The Kaplan-Meier survival curves of spontaneous resolution rates in primary vesicoureteral reflux on medical prophylaxis without surgery (Kaplan-Meier curves show different spontaneous resolution rates of each primary vesicoureterl reflux grade).

median times of SR (38 and 66 months in grade IV and V reflux) were much better than the previous reports. The International Reflux Study in Children (IRSC) reported that the overall and annual SR rate in grade IV reflux were 14% and 3.5%/year in a 5 year follow-up study[1]. The next long-term follow-up study of IRSC showed the increased SR rates to 44% in grade IV reflux at 10 years[4]. The 15 year follow-up study of AUA reported the overall SR rate 35.5%, annual SR rate 5% and estimated median time 9.5 years in grade IV reflux and no spontaneous resolution in grade V reflux[5]. More recent studies reported the estimated median time in grade IV/V reflux was 156 (122-189) months[6] and the SR rates of grade IV reflux were 38-43% at 10 years[7]. The previous studies recruited the children with grade I-IV reflux in majority and only a few studies included a small number of grade V reflux because of early surgical interventions. Therefore, there was scant data in grade V reflux. However, the more recent study showed that severe neonatal reflux (grade IV and V) spontaneously resolved in 38-44% even after a short-term (15 months) follow-up[8,9] and severe infantile VUR (grade IV and V) also spontaneously resolved in 29% during the infant year and then 9% per year afterwards[10]. Those relatively high SR rates of neonatal and infantile primary VUR were similar to our results. This may be related to the age of our patients whose mean age was 18.4 months.

The second concern in severe primary VUR was progressive renal scarring by recurrent pyelonephritis, which was another important reason for early surgical intervention in severe reflux[1-3]. However, there is no sufficient data to conclude the incidence of new renal scars in severe reflux. Reported data about the incidence of new renal scars in severe reflux were not enough and variable which usually included mild reflux. Silva et al reported that incidence of new renal scars was 5.1% in patients with grade II-V reflux, who were followed up for a mean time of 76 (6-411) months and all new renal scars were mild and focal[6]. The Swedish trial reported 7.6% of new renal scar in grade III/IV reflux [23,24] and the randomized intervention of children with VUR (RIVUR trial) reported 12.9% in antibiotic prophylaxis and 10.2% in placebo in grade I-IV reflux[25]. A randomized double blind placebo controlled trial in India reported 16.2% in antibiotic prophylaxis and 16.3% in placebo at 12 months[26]. In this study, the incidences of new renal scars were 10.5% in grade IV reflux and 18.2% in grade V reflux, which were not higher than the previous reports considering the severity of reflux. Compared to congenital renal scars (small scarred kidneys) which were severe and common in neonatal grade IV and V reflux, acquired renal scars in severe reflux were proved to be mild and relatively uncommon events[8,9,13]. Also, the incidence of new renal scars was not different between antibiotic prophylaxis and placebo[25,26], between the surgical intervention and the medical prophylaxis[19] and between antibiotic and probiotics prophylaxis[27,28].

There are two limitations of our study. One is that it was a retrospective study with probable bias, and the other is that there are relatively small numbers of grade V reflux. What makes this study more valuable is that most of the patients with severe reflux were followed up without surgery as possible.

In conclusion, the SR rate of severe primary VUR was higher than reported and new renal scars were minimal even with probiotic prophylaxis. The long-term follow-up on probiotic prophylaxis without surgery can be considered. More evidence is required to revise surgical indications for severe primary VUR.

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