Original Article

J Babol Univ Med Sci
Vol 18, Issu 4; Apr 2016. P:29-34

Spontaneous Vesicoureteral Reflux Resolution among Infants Aged Less Than One Year

H. Sorkhi (MD)*[1], P. Poordadash [2], M. Hajiahmadi (PhD)[1], H. Shafi (MD)[3]

1.Non-Communicable Pediatric Diseases Research Center, Babol University of Medical Sciences, Babol, I.R.Iran
2.Student Research Committee, Babol University of Medical Sciences, Babol, I.R.Iran
3.Fatemeh Zahra Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol, I.R.Iran

J Babol Univ Med Sci; 18(4); Apr 2016; PP: 29-34
Received: Dec 8th 2015, Revised: Jan 6th 2016, Accepted: Mar 2th 2016.

ABSTRACT

BACKGROUND AND OBJECTIVE: Vesicoureteral reflux (VUR) followed by urinary tract infection (UTI) is a major contributing factor to kidney failure, especially during early childhood. This study aimed to evaluate the possibility of spontaneous high-grade VUR resolution in infants aged less than one year.

METHODS: This cross-sectional study was conducted at Amirkola Children's Hospital of Babol, Iran on all the infants aged less than one year with high-grade VUR (III-V). Infants were followed-up in terms of at least one kidney per age, reflux grade, and kidney failure for two years. Evaluation of reflux resolution was performed using voiding cystourethrography (VCUG) and radionuclide cystography (RNC) each year. In addition, presence of kidney failure was assessed via dimercaptosuccinic acid (DMSA) scan within at least 4-6 months after the last UTI diagnosis. Data analysis was performed in SPSS V.22 using Chi-square and Kaplan-Meier survival analysis, and P value of less than 0.05 was considered statistically significant.

FINDINGS: In total, 97 kidneys in 49 infants were evaluated (one infant had only one kidney). Among the studied patients, 29 infants (59.2%) were female, and mean age of the study population was 5.9±3.66 months. Out of 49 infants with VUR, complete recovery was observed in 33 cases (67.3%), while partial resolution (reduced grade of reflux) was reported in 13 cases (26.5%), and lack of resolution was observed in 3 cases (6.1%).

CONCLUSION: According to the results of this study, spontaneous resolution of high-grade VUR could occur in a high percentage of infants aged less than one year. Therefore, it is recommended that early surgical operation be reconsidered for this patient population.

KEY WORDS: *Infants, Spontaneous resolution, Urinary tract infection, Vesicoureteral reflux, Children.*

Please cite this article as follows:

Sorkhi H, Poordadash P, Hajiahmadi M, Shafi H. Spontaneous Vesicoureteral Reflux Resolution among Infants Aged Less Than One Year. J Babol Univ Med Sci. 2016;18(4):29-34.

***Corresponding author: H. Sorkhi (MD)**
Address: Non-Communicable Pediatric Diseases Research Center, Babol University of Medical Sciences, Babol, I.R Iran
Tel: +98 11 32340755
E-mail hadisorkhi@yahoo.com

[DOR: 20.1001.1.15614107.1395.18.4.4.4]
[DOI: 10.22088/jbums.18.4.29]

Introduction

Vesicoureteral reflux (VUR) is defined as the backflow of urine from the bladder into the ureters and kidneys, which primarily occurs due to the failure of the valve at the ureteral-bladder junction. This disorder could be caused by the insufficient intravesical tunneling of the ureter at the ureteral-bladder junction (1). As such, development of the bladder and its volume over time could increase the intravesical tunnel length, leading to the spontaneous resolution of VUR (2).

In VUR, size of distal ureter muscles at the ureteral-bladder junction reduces, which leads to the deficient contraction of this area during urination and retrograde of the urine from the ureters to bladder. Spontaneous resolution of VUR could occur as a result of the development and reconstruction of these muscular fibers over time (3,4).

According to statistics, prevalence of reflux has been estimated at 0.4-1.8%, while. It has been reported to be higher among female infants compared to male ones (ratio: 2.2:0.6). The prevalence of reflux following urinary tract infection (UTI) has been reported to be 31%, while it has been estimated at 20% in patients with prenatal hydronephrosis.

Moreover, the prevalence of reflux is inversely correlated with age. Spontaneous resolution of reflux could be achieved with age (5-7). VUR is considered to be a predisposing factor for UTI, which could bring of the most complications such as pyelonephritis, renal scarring, reflux nephropathy, and high blood pressure (8). In one study, UTI was confirmed as the most common cause of kidney failure (9). Renal scarring associated with VUR may occur in different age groups at variable grades of reflux; however, almost half the cases with renal scarring have been observed at higher grades of reflux (10). Incidence rate of renal scarring associated with UTI has been estimated at 19.4-30%, the risk of which increases at high grades of reflux (11-13).

Considering the long-term complications in VUR and high possibility of spontaneous resolution, low-dose daily antibiotic has been proposed as an effective therapeutic measure in this regard. The annual resolution rate of reflux has been reported to be 5-13%; therefore, prevention of UTI through antibiotic use could maintain the sterile status of urine until complete recovery (14,15).

According to the results of one study conducted on children receiving treatment with cotrimoxazole prophylaxis, patients with renal scarring were diagnosed with higher grades of reflux, and spontaneous resolution was less likely in cases with reflux accompanied by renal scarring and which was associated with a higher risk of recurrent UTI (16). In another study in this regard, rate of spontaneous resolution of reflux was reported to be 38% among children with high-grade VUR (III-V) (reduced reflux grade to I and II).

Furthermore, complications such as recurrent febrile UTI, bladder dysfunction, higher reflux grade, structural renal disease, kidney dysfunction, increased bladder capacity, increased residual urine volume, and passive reflux were reported to have significant adverse effects on the spontaneous resolution of VUR (17). Given the importance of the early diagnosis of VUR in young children in order to prevent the associated complications, various studies have investigated the diagnostic methods and prognostic factors involved in the spontaneous resolution of this disease. Since researchers have not reached a consensus on the prediction of spontaneous resolution of VUR and due to the lack of conclusive findings regarding the influential factors in this process, this study aimed to evaluate the rate of spontaneous resolution of high-grade VUR in infants aged less than one year that admitted in Amirkola Children's Hospital of Babol city, Iran.

Methods

This cross-sectional analytical study was conducted on infants aged less than one year (11 months and 29 days) who were referred to the nephrology department of Amirkola Children's Hospital due to different conditions (e.g., hydronephrosis and UTI) during 1992-1996. VUR of grade III or higher in one or both kidneys was diagnosed in these infants via voiding cystourethrography (VCUG) and radionuclide cystography (RNC). In this study, 49 infants (29 female and 20 male) with VUR were followed-up for two years. Follow-up of the patients was performed using ultrasound (every 3-6 months), VCUG or RNC (each year), and dimercaptosuccinic acid (DMSA) scan (in case of UTI at 4-6 months after UTI or following VUR diagnosis).

Complete recovery was defined as the resolution of reflux, while reduced reflux grade was interpreted as partial recovery, and lack of recovery was referred to the unchanged reflux grade. Exclusion criteria of the

[DOR: 20.1001.1.15614107.1395.18.4.4.4]
[DOI: 10.22088/jbums.18.4.29]

study were undergoing surgery due to secondary causes of reflux (e.g., neurogenic bladder and posterior urethral valves) and patients without an adequate follow-up. Based on the International Classification of VUR, reflux in the infants was categorized into grades I-V (18). During the follow-up, all the patients received daily treatment with low-dose prophylactic antibiotics in order to prevent UTI. Data analysis was performed in SPSS V.22 using Chi-square and Kaplan-Meier survival analysis, and $p<0.05$ was considered statistically significant.

Results

In total, 49 infants were enrolled in this study, including 29 females (59%) and 20 males (41%). Minimum and maximum age of the infants was one day and 12 months, respectively (mean age: 22.9±3.66 months). With regard to the cause of referral, 37 cases (75.5%) had UTI, 11 cases (22.5%) had prenatal hydronephrosis, and in one case (2%) was diagnosed for evaluation of accidental detection of hydronephrosis after abdominal ultrasonography. In this study, mean duration of follow-up was 22.9±13.96 months. In 13 infants(26.5%), the reflux was unilateral, while it was bilateral in 36 cases (73.5%).

Considering the presence of one case with right nephrectomy, we evaluated a total of 97 kidneys. Among these samples, 15 units (15.5%) had grade II VUR, 50 cases (51.5%) had grade III VUR, 16 units (16.5%) had grade IV VUR, 4 cases (4.1%) had grade V VUR, and 12 units(12.4%) were without reflux. Among 49 infants, 33 cases(67.5%) made complete recovery, 13 patients (26.5%) had partial recovery, and 3 cases (6%) had no improvement in VUR. Out of 70 kidneys with grade III and IV of VUR, complete resolution was seen in 47 units(67%), while partial resolution was observed in 15 cases(19%), and lack of reflux resolution was showed in eight kidneys(14%) ($p<0.05$) (table 1). Out of 29 female infants with reflux, 19 patients (65.5%) had complete recovery, while 7 subjects (24%) had partial recovery. As for the male infants with reflux (n=20), 14 cases (70%) had complete recovery, and 6 subjects (30%) had partial recovery. Out of 37 infants with initial UTI, 26 cases (70%) made complete recovery, while 8 patients (21.5%) had partial recovery. Among 11 infants presented with prenatal hydronephrosis, six cases (54.5%) had complete recovery, while five subjects (45.5%) had partial recovery.

Furthermore, all the infants with unilateral reflux (n=13) had complete resolution, while out of 36 patients with bilateral reflux, 20 cases (55.5%) had complete resolution, and 13 subjects (36%) had partial resolution. The rate of resolution in unilateral reflux was significantly higher compared to bilateral reflux ($p<0.05$) (table 2). Out of 85 kidneys with VUR, 77 cases were followed-up via DMSA scan. Parenchymal damage was detected in 41 units (56%) with grade III (or higher) VUR, while no such damage was observed in 23 unites. (44%). In the comparison of the different grades of reflux and renal parenchymal disease based on DMSA scan, 77 kidneys were evaluated in this study. Renal parenchymal disease was observed in 28 of 47 kidneys with grade III reflux, 10 of 14 units with grade IV reflux, and all the cases with grade V reflux. Moreover, among the cases with renal parenchymal defects in DMSA scan (n=41), 28 units (68%) had complete resolution, 8 cases (19.5%) had partial resolution, and 5 units (12.5%) had no improvement. As for the kidneys without parenchymal defect (n=23), 16 units (69.5%) had complete resolution, 5 cases (21.5%) had partial resolution, and 2 units (9%) had no improvement.

In this regard, no significant correlation was observed between the extent and location of renal parenchymal involvement and reflux resolution rate. It is also noteworthy that over time, VUR was resolved in a significant proportion of the evaluated kidneys (fig1).

Table 1. Relationship between resolution rate and reflux grade in infants with vesicoureteral reflux aged less than one year

Resolution / Reflux Grade	Complete	Partial	No Resolution	Total
III	39	8	3	50
IV	6	6	4	16
V	2	1	1	4
Total	47(67)	15(21.5)	8(11.5)	70

p<0.05

[DOR: 20.1001.1.15614107.1395.18.4.4.4]
[DOI: 10.22088/jbums.18.4.29]

Table 2. Relationship between reflux resolution, gender, type of reflux, and cause of referral in infants with vesicoureteral refluxaged less than one year

Variable	Resolution	Complete N(%)	Partial N(%)	No Resolution N(%)	Total N(%)	P-value
Gender	Female	19(65.5)	7(24)	3(10.5)	29(100)	>0.05
	Male	14(70)	6 (30)	-	20(100)	
Type of Reflux	Unilateral	13(100)	-	-	13(100)	<0.05
	Bilateral	20(55.5)	13(36)	3(8.5)	36(100)	
Cause of Referral	Urinary Tract Infection	26(70)	8(21.5)	3(8.5)	37(100)	
	Hydronephrosis	6(54.5)	5(45.5)	-	11(100)	>0.05
	Other	1(100)	-	-	1(100)	

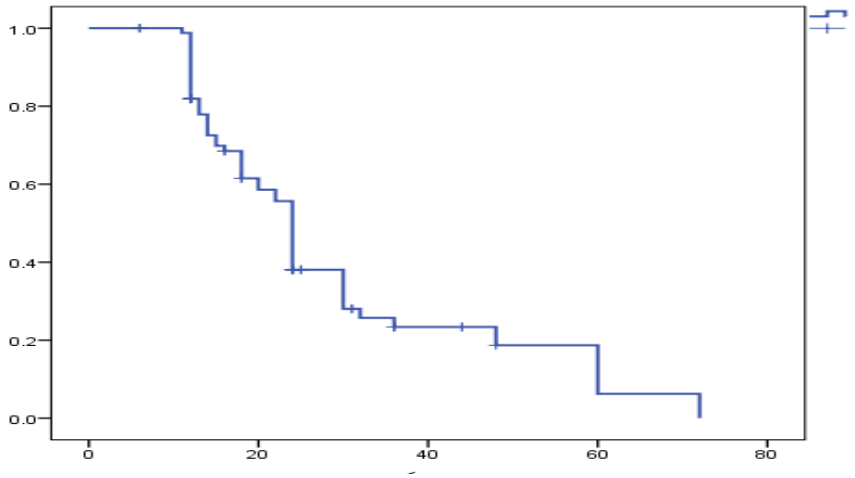

Figure 1. Resolution and lack of resolution of vesicoureteral reflux in infantsaged less than one year based on studied kidney units

Discussion

In the present study, complete resolution of VUR was seen in 33 infants aged less than one year (67.3%), and it was observed in 57 kidneys unites (67.1%) with reflux. According to one study conducted in this regard, the resolution rate of reflux was 38.6% in infants aged less than one year, and then 40%. Also a follow-up period was 11-132 months (19). In another study performed on infants aged less than one year, improvement of grade III-V reflux was reported in 38% of the cases within an average follow-up period of 36 months (17). In a study by Sharbafet al., spontaneous reflux resolution rate was reported to be 55% within a follow-up period of 4.5 years (20).

Furthermore, the results of another research by Martin et al. indicated the rate of recovery to be 64% among 80 infants aged less than six months (113 kidney unite) (21). Based on the findings of the aforementioned studies, spontaneous resolution of VUR could occur in a large proportion of infants over time. However, the higher percentage of recovery in the present study is noteworthy, and to evaluation of this difference, further investigations are required on larger sample sizes.

According to the findings of the current study, 65.5% of female infants and 70% of male infants with VUR had spontaneous resolution of the reflux, and no significant difference was observed between the two genders in this regard. Similarly, Sjostrom et al. reported no statistically significant difference between the two genders of infants with respect to the rate of spontaneous reflux resolution.

It should be noted that the spontaneous resolution rate of high-grade VUR (IV and V) has been shown to be significantly higher in male infants compared to female ones (17). Correspondingly, the results obtained by Schwab et al. indicated the resolution rate of VUR to be higher among male infants (15). On the other hand, in a report by Hu, no significant correlation was found between the gender and spontaneous reflux resolution rate of infants (22). Based on the

[DOR: 20.1001.1.15614107.1395.18.4.4.4]
[DOI: 10.22088/jbums.18.4.29]

aforementioned findings, it could be concluded that gender could not be a predictive factor for the rate of spontaneous reflux resolution in patients with VUR. In the present study, we also evaluated the association between VUR, kidney failure, and possibility of spontaneous reflux resolution. According to our findings, 68% of the studied kidneys with VUR and renal failure, as well as 72% of the kidneys with reflux and without failure, had spontaneous resolution.

Although statistics are indicative of the possibility of spontaneous resolution in kidneys with reflux and without renaldamage, no significant difference has been reported between these cases in this regard. According to the findings of Martin et al., abnormal DMSA scan, grade V reflux, and febrile UTI were proposed as the predictors of lack of reflux resolution and need for surgery (21). In another study by Jeon et al., renal scarring was reported to be negatively associated with the spontaneous resolution of reflux. Moreover, rate of recovery was observed to be lower in infants with reflux and kidney damage (16). Differences in the results of the aforementioned studies could be due to the variable definition and extent of renal scarring, as well as the time of DMSA scan, which might have affected the statistical rates of reflux resolution. According to the results of the current study, reflux grade and possibility of spontaneous reflux resolution were negatively correlated. In other words, higher grades of reflux were associated with the lower possibility of spontaneous resolution.

In study by Zerati Filho et al., possibility of spontaneous reflux resolution was higher in lower grades (I and II) compared to higher grades of reflux (III and IV) (10). Similarly, the findings of Sharifian et al. were indicative of the lower rate of spontaneous resolution in higher grades of reflux (23). Furthermore, the results obtained by Vachvanichsanonget al. confirmed that the possibility of spontaneous resolution was higher in reflux grades of I-III compared to grades IV and V (24). However, the findings of Schwab et al. were indicative of no significant difference in the rate of spontaneous resolution in lower reflux grades (I-III) (15). Based on the findings of the aforementioned studies, it could be concluded that the possibility of spontaneous resolution is relatively higher in lower reflux grades over time. According to the present study, reflux diagnosed in 75.5% and 24.4%of the infants by UTI and prenatal hydronephrosis, respectively. However, no statistically significant difference was observed between the cause of referral and possibility of reflux resolution, which is consistent with the findings of Sjostrom et al. (17). On the other hand, the results obtained by Martin et al. indicated that history of prenatal hydronephrosis and UTI was associated with a lower possibility of spontaneous reflux resolution in infants (21). In the current research, a significant proportion kidneys with reflux were recovered over time. Sjostrom et al. investigated the associations between bladder dysfunction, bladder capacity, residual urine volume and renal disorders. According to the findings, these factors hindered the spontaneous resolution of reflux.

Additionally, passive reflux and UTIs negatively affected the Kaplan-Meier curves and were associated with lower resolution rate of VUR (17). With regard to the spontaneous resolution rate of unilateral and bilateral reflux, the results of the present study indicated that the possibility of resolution was significantly higher in patients with unilateral reflux (Curve 3). This is consistent with the findings of Vachvanichsanong et al. (24) , that the rate of spontaneous resolution was higher in patients with unilateral reflux compared to those with bilateral reflux. Therefore, it could be concluded that over time, spontaneous reflux resolution could occur in a large proportion of kidneys with unilateral reflux.

In conclusion, the results of the current study indicated that a high percentage of infants aged less than one year with reflux could have spontaneous resolution over time. Therefore, it is recommended that early surgical operation could not be reconsidered for this patient population. Furthermore, it was observed that the presence of congenital hydronephrosis and referral due to UTI may not affect the prognosis of spontaneous reflux resolution, and spontaneous resolution is likely to occur in such cases as well.

Acknowledgments

Hereby, we extend our gratitude to the Deputy of Research and Technology at Babol University of Medical Sciences for the financial support of this study. We would also like to thank the Non-communicable Pediatric Diseases Research Center and Clinical Research Development Center of Amirkola Children's Hospital for assisting us in this research project.

[DOR: 20.1001.1.15614107.1395.18.4.4.4]
[DOI: 10.22088/jbums.18.4.29]

References

1.Tanagho E, Guthrie T, Lyon R. The intravesical ureter in primary reflux. J Urol. 1969;101(6):824-32.
2.Stephens FD, Lenaghan D. The anatomical basis and dynamics of vesicoureteral reflux. J Urol. 1962;87:669-80.
3.Radmayr C, Fritsch H, Schwentner Ch, Lunacek A, Deibl M, Bartsch G, et al. Fetal development of the vesico-ureteric junction, and immunohistochemistry of the ends of refluxing ureters. J Pedia Urol. 2005;1(2):53-9.
4.Radmayr C, Schwentner C, Lunacek A, Karatzas A, Oswald J. Embryology and anatomy of the vesicoureteric junction with special reference to the etiology of vesicoureteral reflux. Ther Adv Urol. 2009;1(5):243-50.
5.Eccles M, Jacobs G. The genetics of primary vesico-ureteric reflux. Ann Acad Med, Singapore. 2000;29(3):337-45.
6.Chand DH, Rhoades T, Poe SA, Kraus S, Strife CF. Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. J Urol. 2003;170(4):1548-50.
7.Sorkhi H, Nooreddini HN, Amiri M, Osia S, Farhadi-Niakee S. Prediction of Vesicoureteral Reflux in Children with First Urinary Tract Infection by Dimercaptosuccinic Acid and Ultrasonography. Iran J Pediatr. 2012;22(1):57-62
8.Hellström A, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child. 1991;66(2):232-4.
9.Sorkhi H, Bijani A. Causes of chronic renal failure in 85 children who referred amirkola children hospital. J Babol Univ Med Sci. 2006:8(5): 35-9.[In Persian]
10.Zerati Filho M, Calado AA, Barroso Jr U, Amaro JL. Spontaneous resolution rates of vesicoureteral reflux in Brazilian children: a 30-year experience. Int Braz J Urol. 2007;33(2):204-15.
11.Yılmaz S, Özçakar ZB, Kurt Şükür ED, Bulum B, Kavaz A, Elhan A.H, et al. vesicoureteral reflux and renal scarring risk in children after the first febrile urinary tract infection. Nephron. 2016;132(2):175-80.
12.Mattoo TK, Chesney RW, Greenfield SP, Hoberman A, Keren R, Mathews R, Gravens Mueller L, et al Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. Clin J Am Soc Nephrol. 2016; 11(1):54-6113.
13.Sorkhi H, Rajifar B. Vesicoureteral Reflux and Renal Scarring in Infants. J Babol Univ Med Sci. 2010:12(2);42-6.
14.Greenfield SP, Wan J. Resolution rates of low grade vesicoureteral reflux stratified by patient age at presentation. J Urol. 1997;157(4):1410-3.
15.Schwab CW, Wu HY, Selman H Grahame H, Howard M, Douglas A, et al. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. J Urol. 2002;168(6):2594-9.
16.Jeon JH, Lee KH, Park JS. The effect of renal scarring on spontaneous resolution and breakthrough infection in children with vesicoureteral reflux. Korean J Urol. 2009;50(7):699-703.
17.Sjöström S, Sillén U, Jodal U, Sameby L, Sixt R, Stokland E, et al. Predictive factors for resolution of congenital high grade vesicoureteral reflux in infants: results of univariate and multivariate analyses. J Urol. 2010;183(3):1177-84.
18.Lebowitz R, Olbing H, Parkkulainen K, Smellie J, Tamminen-Möbius T. International system of radiographic grading of vesicoureteric reflux. Pediatr Radiol. 1985;15(2):105-9.
19.Wildbrett P, Schwebs M, Abel J, Lode H, Barthlen W. Spontaneous vesicoureteral reflux resolution in children: A ten-year single-centre experience. Afr J Paediatr Surg. 2013;10(1):9-12.
20.Sharbaf FG, Fallahzadeh MH, Modarresi AR, Esmaeili M. Primary vesicoureteral reflux in Iranian children. Indian Pediatr. 2007;44(2):128-30.
21.Martin AD, Iqbal MW, Sprague BM ,Mireya Diaz H, Rushton G, Craig A. Peters, et al. Most infants with dilating vesicoureteral reflux can be treated nonoperatively. J Urol. 2014;191(5):1620-7.
22.Hu C, Peng NJ, Lin HS, Chiou YH. Predict the spontaneous resolution of vesicoureteral reflux by direct radionuclide cystography. Rev Esp Med Nuc Imagen Molecul. 2013;32(2):65-9.
23.Sharifian M, Boroujerdi HZ, Dalirani R Maham S, Akhavan M, Karimi A,et al. Spontaneous resolution of vesicoureteral reflux (VUR) in Iranian children: A single center experience in 533 cases. Nephro-Urol Mon. 2011; 3(3):191-5.
24.Vachvanichsanong P, Dissaneewate P, Lim A, Geater A. Outcome of conservative treatment of primary vesicoureteral reflux in 87 Thai children in a single center. Inter J Urol. 2006;13(11):1393-7..

[DOR: 20.1001.1.15614107.1395.18.4.4.4]
[DOI: 10.22088/jbums.18.4.29]