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The Value of Estimation of Distal Ureteral Dilatation in Primary Vesicoureteral Reflux

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Purpose: Recently, several studies have suggested that distal ureteral dilatation is an important factor influencing the spontaneous resolution of primary vesicoureteral reflux (VUR). We evaluated the relationship between distal ureteral dilatation and the spontaneous resolution of primary VUR.

Materials and Methods: The medical records of 114 patients with primary VUR maintained on prophylactic antibiotics from April 1999 to August 2008 were retrospectively reviewed. The patients' mean age was 24.2 months (range, 6-108 months). There were 66 male patients and 48 female patients. The mean follow-up was 37.6 months (range, 12-102 months). We analyzed various factors including age, gender, grade of reflux, laterality, and ureteral diameter ratio (UDR; the largest ureteral diameter was divided by the distance from the L1-4 vertebral body to minimize the differences in diameter by age) to determine whether these factors influenced the spontaneous resolution of primary VUR.

Results: Unilateral, low-grade reflux and low UDR were significantly associated with the spontaneous resolution of reflux ($p=0.048$, $p<0.001$, and $p<0.001$, respectively). The multivariate analysis revealed that the spontaneous resolution rate of primary reflux was significantly higher in patients with low UDR than in patients with high UDR ($p<0.001$).

Conclusions: The degree of distal ureteral dilatation is expected to be another important factor in determining therapeutic course and predicting the spontaneous resolution of VUR.

Key Words: Ureter; Vesico-ureteral reflux

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INTRODUCTION

Vesicoureteral reflux (VUR) is a relatively common disease in children; the onset rate in children ranges from 0.4% to 1.8% [1]. VUR is diagnosed by voiding cystourethrography, and the severity of reflux is graded in accordance with the standards of the International Reflux Study in Children (IRSC) [2].

The reflux grade is an important diagnostic method for determining the treatment and prognosis of VUR. In lower grade VUR, relatively more patients experience spontaneous resolution. Therefore, patients who are determined to have lower grade VUR tend to be treated conservatively until the VUR resolves. However, there has been much controversy concerning the treatment guidelines for grade III and IV reflux. To this end, Smellie et al reported that pa-

tients with high-grade VUR often have spontaneous resolution of VUR [3]. Furthermore, many arguments have been made as to whether the existing grades are suitable for predicting the spontaneous resolution of VUR. In addition to reflux grade, it has also been reported that age, laterality (unilateral or bilateral), and gender exert an influence on the spontaneous resolution of reflux [4].

In addition to the existing prognostic factors and reflux grades, other factors have recently been reported [5,6]. In particular, we have focused on the recent literature that VUR is influenced by the severity of distal ureteral dilatation and analyzed the degree with which distal ureteral dilatation influenced the spontaneous resolution of VUR to ascertain whether ureteral dilatation is as valuable a prognostic factor as the ones currently in existence.

MATERIALS AND METHODS

This study retrospectively analyzed how the degree of distal ureteral dilatation influenced the spontaneous resolution of VUR. Between April 1999 and August 2008, a total of 114 patients who were diagnosed with primary VUR and were managed with prophylactic antibiotics were included in this study. Patients with congenital anomalies and functional disorders in the urinary tract, such as congenitally malformed urethra, neurogenic bladder, double ureters and urethral valve, hutch diverticulum, and refluxing megaureter, were excluded from this study. The patients' mean age was 24.2 months (range, 6-108 months). Male and female patients numbered 66 and 48, retrospectively. The mean follow-up duration was 37.6 months (range, 12-102 months), and there were 75 and 39 cases of unilateral and bilateral VUR, respectively. There were 10, 32, 39, 20, and 13 cases each of grade I, II, III, IV, and V reflux, respectively (Table 1).

The degree of distal ureteral dilatation was analyzed as the longest diameter from among the distal ureters between the sacroiliac joint and the ureterovesical junction on voiding vesicourethrography. To correct the ureteral diameter, which may change as a child grows, the ureteral diameter ratio was calculated by dividing the maximum diameter of the distal ureter by its distance from the first lumbar vertebra to the fourth lumbar vertebra. We selected lumbar spine length to correct the ureteral diameter because Currarino et al reported that there is linear growth of the spine from birth to 16 years, and the rib, scapula, other bones screen the thoracic spine on voiding vesicourethrography [7]. The correlation between the ureteral diameter ratio and spontaneous resolution was analyzed. For conservative treatment, prophylactic antibiotics were used. Because it is believed that VUR is a predisposing factor for urinary tract infection, which in turn may cause permanent renal injury, voiding cystourethrography was per-

formed on all subjects at intervals of 6 months or 1 year. Cases for which VUR was not observed on the voiding cystourethrography were defined as spontaneous resolution.

The correlation between each factor and spontaneous resolution was analyzed through both univariate analysis and multivariate analysis. For statistical analysis, the SAS software (version 9.1.2; SAS Institute, Cary, NC, USA) was used; chi-squared test, p for trend, Spearman rank correlation, and a logistic regression model were performed. Cases for which the p-values were less than 0.05 were considered statistically significant.

RESULTS

Spontaneous resolution occurred in 57 (50%) of 114 cases. Surgical operations were performed on 44 (38%) of the other 57 cases in which reflux had already progressed or had not changed. Medical treatment with prophylactic antibiotics and follow-ups were performed on the residual 13 cases (10%). There were 65 cases aged less than 1 year and 49 cases aged over 1 year; of those less than 1 year of age, 35 cases (53%) showed spontaneous resolution, and of those aged 1 year or older, 22 cases (44%) showed spontaneous resolution. However, this difference was not statistically significant (p=0.344). Additionally, spontaneous resolution occurred in 28 of 66 males (42%) and in 29 of 48 females (60%) (p=0.057). Spontaneous resolution occurred in 42 of 75 cases (56%) of unilateral VUR and in 15 of 39 cases (38%) of bilateral VUR (p=0.048). In each grade (I to V), 7 cases (70%), 23 cases (71%), 21 cases (53%), 5 cases (25%), and 1 case (8%) had spontaneous resolution, respectively, demonstrating that spontaneous resolution rates were higher in the lower grades (p < 0.001) (Table 2). The mean ureteral diameter ratio was 0.073 (range, 0.004-0.216), and the univariate and multivariate analyses showed that the spontaneous resolution rate significantly increased as the ureteral diameter

TABLE 1. Characteristics of 114 patients with primary vesicoureteral reflux

Characteristics	No. of patients
No. of patients	114
Mean age (months)	24.2 (6-108)
Sex	
Male	66
Female	48
Mean duration of treatment (months)	37.6 (12-102)
Laterality	
Unilateral	75
Bilateral	39
Grade	
I	10
II	32
III	39
IV	20
V	13

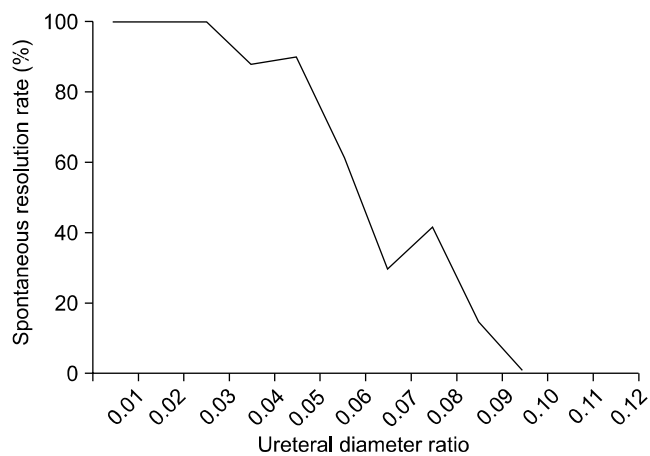
TABLE 2. Relationship between spontaneous resolution and age, sex, laterality, and reflux grade

Factors	No. of patients	Spontaneous resolution (%)	p-value
Age (years)			0.334
< 1	65	35 (53)	
≥ 1	49	22 (44)	
Sex			0.057
Male	66	28 (42)	
Female	48	29 (60)	
Laterality			0.048
Unilateral	75	42 (56)	
Bilateral	39	15 (38)	
Grade			<0.001
I	10	7 (70)	
II	32	23 (71)	
III	39	21 (53)	
IV	20	5 (25)	
V	13	1 (8)	

TABLE 3. Multivariate analysis by the logistic regression model

Risk factors	Odds ratio	95.0% CI ^a	p-value
Age	3.032	0.967-9.510	0.0572
Sex	0.476	0.149-1.525	0.2115
Laterality	1.021	0.322- 3.237	0.9715
VUR Grade			0.8389
II	0.933	0.138-6.281	
III	0.522	0.078-3.495	
IV	0.674	0.072-6.330	
V	0.195	0.007-5.712	
Ureteral diameter ratio	4.479x10 ³²	1.059x10 ¹⁸ -1.167x10 ³⁹	<0.001

VUR: vesicoureteral reflux, ^a: confidence interval

**FIG. 1.** Relationship between spontaneous resolution and ureteral diameter ratio.

ratio decreased ($p < 0.001$) (Table 3, Fig. 1). Furthermore, there was a statistical correlation between ureteral diameter ratio and VUR grade ($p < 0.001$, $r_s = 0.643$).

DISCUSSION

It is well known that age, gender, laterality, and reflux grade have a large influence on the occurrence of spontaneous resolution in patients with primary VUR. With respect to age, the spontaneous resolution rate is higher in younger patients. Yeung et al demonstrated that in 155 patients with primary VUR, the spontaneous resolution rate was higher in high-grade patients aged less than 1 year than in those older than 1 year [8]. Park et al who performed conservative treatments of 48 cases of ureteral reflux for 35 months (on average), reported that reflux spontaneously resolved in 27 cases and that the resolution rate was higher in younger patients, despite higher grades of reflux [9]. It is thought that the immature muscles of the vesical trigone develop with time and that the submucosal ureter becomes longer. In this study, the spontaneous resolution rate reached 53% and 44% in patients aged less than 1 year and in those aged 1 year and above, respectively.

Although the rate was higher in younger patients, the difference was not statistically significant.

Many studies have suggested that the onset rate of VUR is higher in girls than in boys. Chand et al performed a study with 15,504 children and reported that the onset rate was approximately two times higher in girls less than 2 years of age than in boys of the same age [10]. According to the report by Yeom et al, in general, the onset rate of VUR was higher in girls than in boys; however, in the case of children aged less than 1 year, the rate was higher in boys [11]. In our study, the overall onset rate was higher in boys (57%) than in girls (43%). This may have resulted from the fact that children less than 1 year of age accounted for 44 boys and 21 girls in our study, which means that the onset rate may have been inflated owing to the larger number of boys. With respect to spontaneous resolution, Schwab et al reported that VUR was rapidly resolved in boys compared with girls [12], and Sjöström et al reported that the spontaneous resolution rate of high-grade VUR (at least grade IV) was higher in boys aged less than 1 year than in girls of the same age grouping [13]. In our study, however, it was higher in girls (60%) than in boys (42%), although the difference was not statistically significant. This difference might have resulted from there being more high-grade VUR in boys than in girls.

With regard to the correlation between laterality and spontaneous resolution, Estrada et al reported that unilateral VUR resolved earlier than bilateral VUR [14]. Smellie et al performed a study among children with grade III or IV reflux and reported that the spontaneous resolution rate was significantly higher in unilateral VUR [3]. Tamminen-Möbius et al reported that the spontaneous resolution rate reached 12% in bilateral VUR but was 54% in unilateral VUR [15]. Similarly, in our study, the rate of spontaneous resolution was significantly higher in unilateral VUR than in bilateral VUR (56% vs. 38%, $p = 0.048$).

Zerati Filho et al researched spontaneous resolution rates in 417 children for 2.7 years (on average), and found resolution rates of 87.5%, 77.6%, 52.8%, 12.2%, and 4.3% for grade I, II, III, IV, and V reflux, respectively [16]. Arant reported that the spontaneous resolution rate reached 80% in grade I and II primary VUR without operative management [17]. Schwab et al performed a study with 214 children and showed that the spontaneous resolution rate was 13% in low-grade VUR (grade III and less) and 5% in high-grade VUR (grade IV and over) [12]. Barroso et al observed 178 children with unilateral VUR for 55 months on average and reported that there was a strong possibility that high-grade VUR could develop into bilateral VUR [18]. In our study, 69% of low-grade VUR (grade II or less) spontaneously resolved; however, for high-grade VUR (grade IV and over), the spontaneous resolution rate was just 18%, showing the inverse relationship between the spontaneous resolution rate and the reflux grade.

Concerning primary VUR, there have been two dominant views. One is that the antireflux function is weakened due to the congenitally immature muscles that go from the

vesical trigone to the terminal ureter. The other is that the ureterovesical junction, formed from the outside in during fetal life, makes the submucosal ureter shorter and causes VUR [4]. Specifically, the length and diameter of the submucosal ureter may be a large part of primary VUR. However, the reflux grade is used to evaluate the severity of primary VUR, a grading system that reflects the structure of the upper urinary system, including the renal pelvis and the renal calyx, and the subjective judgement of the person making the evaluation is reflected in grading. On the authority of such hypotheses, we calculated the ureteral diameter ratio by dividing the maximum diameter of the distal ureter by the distance from the first lumbar vertebra to the fourth one so as to correct the ureteral diameter for change with child growth. We then analyzed the relationship between the ureteral diameter ratio and spontaneous resolution. Few studies have been carried out about distal ureteral dilatation as a factor influencing the spontaneous resolution of primary VUR. Méndez et al classified patients into three groups according to how much the lower ureter was dilated on ultrasonography and analyzed the prognoses after ureteral submucosal injection [5]. They reported that distal ureteral dilatation was an important prognostic factor in treating primary reflux. Lee et al divided the maximum length of the lower ureter, as measured by preoperative voiding cystourethrography using the length of the fourth lumbar vertebra, and performed ureteral submucosal injection according to the calculated ratio and analyzed its relationship to the recurrence of VUR [6]. The results showed that the dilatation of the lower ureter was a significant prognostic factor. We analyzed the influence of distal ureteral dilatation on the spontaneous resolution of VUR, through univariate analysis based on the logistic regression model and multivariate analysis from which age, gender, laterality, and reflux grade were excluded. As a result, we determined that the ureteral diameter ratio was significantly related to the spontaneous resolution of reflux. Thus, it appears that the ureteral diameter ratio may objectively measure vesicoureteral structure and thus may be an appropriate index to predict not only the present state of VUR but also the possibility of spontaneous resolution.

CONCLUSIONS

We have presented the degree of distal ureteral dilatation, which has the benefit of predicting spontaneous resolution more objectively. Distal ureteral dilatation may be another prognostic factor in VUR, determining therapeutic course and predicting spontaneous resolution of VUR.

Conflicts of Interest

The authors have nothing to disclose.

REFERENCES

1. Bailey R. Vesicoureteric reflux in healthy infants and children. In: Hodson J, Kincaid-Smith P, editors. *Reflux nephropathy*. New York: Masson; 1979;59-61.
2. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. *Pediatr Radiol* 1985;15:105-9.
3. Smellie JM, Jodal U, Lax H, Möbius TT, Hirche H, Olbing H. Outcome at 10 years of severe vesicoureteric reflux managed medically: report of the International Reflux Study in Children. *J Pediatr* 2001;139:656-63.
4. Atla A, Keating MA. Vesicoureteral reflux and megaureter. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. *Campbell's urology*. 9th ed. Philadelphia: Saunders; 2007;3423-81.
5. Méndez R, Somoza I, Tellado MG, Liras J, Sanchez A, Pais E, et al. Predictive value of clinical factors for successful endoscopic correction of primary vesicoureteral reflux grades III-IV. *J Pediatr Urol* 2006;2:545-50.
6. Lee DW, Kang KM, Oh WS, Kim JS, Chung SK. Risk factors for treatment failure after endoscopic subureteral injection of dextranomer/hyaluronic acid copolymer (Deflux®) for vesicoureteral reflux. *Korean J Urol* 2009;50:61-6.
7. Currarino G, Williams B, Reisch JS. Linear growth of the thoracic spine in chest roentgenograms from birth to 16 years. *Skeletal Radiol* 1986;15:628-30.
8. Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. *Br J Urol* 1997;80:319-27.
9. Park SY, Park HY, Woo YN. The factors affecting the outcome after medical management of vesicoureteral reflux. *Korean J Urol* 2006;47:994-1000.
10. 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;170:1548-50.
11. Yeom MH, Chung SK, Lee KS, Kim KS, Park JS, Ryu DS, et al. Incidence of vesicoureteral reflux for prepuberty patients in Daegu city and Gyeongbuk area according to the clinical indications, gender, and age. *Korean J Urol* 2005;46:1284-9.
12. Schwab CW Jr, Wu HY, Selman H, Smith GH, Snyder HM 3rd, Canning DA. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. *J Urol* 2002;168:2594-9.
13. Sjöström S, Sillén U, Bachelard M, Hansson S, Stokland E. Spontaneous resolution of high grade infantile vesicoureteral reflux. *J Urol* 2004;172:694-8.
14. Estrada CR Jr, Passerotti CC, Graham DA, Peters CA, Bauer SB, Diamond DA, et al. Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J Urol* 2009;182:1535-41.
15. Tamminen-Möbius T, Brunier E, Ebel KD, Lebowitz R, Olbing H, Seppänen U, et al. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. *J Urol* 1992;148:1662-6.
16. Zerati Filho M, Calado AA, Barroso U Jr, Amaro JL. Spontaneous resolution rates of vesicoureteral reflux in Brazilian children: a 30-year experience. *Int Braz J Urol* 2007;33:204-12.
17. Arant BS Jr. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. *J Urol* 1992;148:1683-7.
18. Barroso U Jr, Barroso VA, de Bessa J Jr, Calado AA, Zerati Filho M. Predictive factors for contralateral reflux in patients with conservatively treated unilateral vesicoureteral reflux. *J Urol* 2008;180:297-9.