Journal of Pediatric Urology (2011) 7, 612—615

Journal of Pediatric urology

Relationships among vesicoureteric reflux, urinary tract infection and renal injury in children with non-neurogenic lower urinary tract dysfunction

Dinçer Avlan [a], Gökhan Gündoğdu [a], Hakan Taşkınlar [a], Ali Delibaş [b,*], Ali Naycı [a]

[a] Department of Pediatric Surgery, Mersin University, Faculty of Medicine, Mersin, Turkey
[b] Department of Pediatrics, Division of Nephrology, Mersin University, Faculty of Medicine, Mersin, Turkey

Received 1 December 2010; accepted 4 May 2011

KEYWORDS
Voiding dysfunction;
Urinary tract infection;
Vesicoureteric reflux;
Renal scan

Abstract *Objective:* To determine the relationship between vesicoureteric reflux (VUR), urinary tract infection (UTI), renal damage and the pattern of non-neurogenic lower urinary tract dysfunction (LUTD), and to reveal the possible risk factors for renal damage in children with LUTD.
Methods: For the years 2004—2010, demographic, clinical, laboratory and urodynamic study reports of children with LUTD were retrospectively reviewed.
Results: Of 96 patients, there were diagnosed 70 with overactive bladder (OAB), 8 pure dysfunctional voiding (DV) and 18 OAB plus DV. The rate of VUR, UTI and renal damage in patients with OAB plus DV and pure DV was higher than in patients with OAB alone. VUR was significantly higher among the patients who had UTI. Renal scarring was detected in 25 patients, of whom 78% had OAB plus DV and 75% DV. The presence of VUR was associated with a significant increase in the rate of renal damage, and dilating reflux caused significantly greater damage compared to non-dilating reflux.
Conclusion: OAB plus DV and DV are major risk factors for VUR, UTI and renal damage. The presence of VUR in children with LUTD plays an important role with regard to UTI and renal damage, with dilating VUR a major risk factor associated with renal damage.

Introduction

Non-neuropathic or non-anatomic lower urinary tract dysfunction (LUTD) is related to a delay in the maturation of neurological control of the lower urinary tract or abnormal behavior acquired during the training period of

* Corresponding author. Mersin Universitesi Tıp Fakültesi, Çocuk Cerrahisi AD. 33070, Zeytinlibahçe Mersin, Turkey. Tel.: +90 324 337 43 00.
E-mail address: dinceravlan@yahoo.com (A. Delibaş).

1477-5131/$36
doi:10.1016/j.jpurol.2011.05.002

urinary sphincter control [1]. LUTD represents a disturbance of the lower urinary tract dynamics affecting detrusor and ureterotrigonal structure. Increased intravesical pressures in children with LUTD cause distortion of the ureterotrigonal junction and predispose to vesicoureteric reflux (VUR) [2].

Even though the association of VUR, urinary tract infection (UTI) and renal injury is well known [3], current opinion is that VUR alone is not sufficient to cause renal injury. It has been reported that there are close links among VUR, UTI and LUTD [4]. Recurrent UTI has been shown to be higher in VUR patients with LUTD than in VUR children without such dysfunction [5,6]. The children with VUR in association with LUTD may be at increased risk for renal damage given their increased risk of developing UTI. In addition, LUTD plays an important role in renal damage without VUR, so-called non-refluxing pyelonephritis [7]. Although, the many characteristics of the relationships among LUTD, VUR and renal injury have been recently recognized, studies continue to reveal more information.

The aim of this retrospective study was to identify the possible risk factors for renal scarring and the characteristics related to VUR among patients diagnosed with non-neurogenic LUTD.

Patients and methods

We retrospectively examined the medical records of patients with non-neurogenic LUTD seen in our outpatient clinic between 2004 and 2010. Neurologically normal children without any urogenital disorder except VUR were included in the study. Urogenital anatomic conditions (e.g. posterior urethral valve, ureterocele) and anorectal malformations were excluded from the study. The study population consisted of 96 children (71 girls and 25 boys) all of whom were toilet trained. The mean age at admission was 7.9 $\pm$ 2.4 years. The initial evaluation of all patients included a detailed history, voiding diary and clinical examination. A complete urologic investigation, including urinanalysis and culture, voiding cystourethrography (VCUG), renal ultrasound, technetium 99m-dimercaptosuccinic acid (DMSA) renal scan and urodynamic studies (UDS), was performed in all patients. On DMSA renal scan, hypoactive areas, contour defects, renal atrophy and diffuse scarring were defined as renal damage.

UTI was diagnosed by history, clinical symptoms and urine culture. There were caes of recurrent (two or more episodes) febrile UTI among these patients. They also had symptoms or signs suggesting UTI, such as fever, pain, dysuria, nausea, vomiting and smelly urine. Prophylactic antibiotics were started for patients with VUR.

A history of constipation was defined as a stool frequency of less than three times per week, with or without encopresis.

The definitions and methods for UDS suggested by the International Children's Continence Society were used [8]. UDS, including initial uroflowmetry, calculation of residual urine, saline cystometry with simultaneous monitoring of total intravesical, intrarectal and subtracted detrussor pressures, and surface pelvic floor electromyography during bladder filling and voiding, were performed in all patients while they were awake and seated. At least two repeat fillings were performed in each study. Overactive detrusor contraction was defined as any involuntary increase in detrusor pressure greater than 15 cm H_2O in consecutive filling cycles. Any sphincter activity during voiding resulting in a decrease or an interruption of urinary flow was diagnosed as dysfunctional voiding (DV) [8].

VUR was graded according to the International Reflux Study Classification. Patients with grades III, IV, V and bilateral were defined as dilating, while grades I and II were categorized as non-dilating reflux. The distribution of demographic, clinical and urodynamic parameters was compared between the groups.

Statistical analysis

Data were analyzed with commercially available statistical software (SPSS® version 11.5). Mean, standard deviation and percentages were used for descriptive statistics. Group comparisons were performed using the independent *t*-test for continuous data, Mann–Whitney *U*-test for non-continuous data, and the Chi-square test were used for categorical data. A P value of ≤ 0.05 was considered statistically significant.

Results

Urgency, urinary incontinence and holding maneuvers were detected in 62 (64.5%), 52 (54.1%) and 46 (47.9%) patients, respectively, as the lower urinary tract symptoms. Of 96 patients, 45 (46.8%) had a recurrent UTI history. When girls and boys were compared, the rate of girls with a UTI was significantly higher (63% vs 37%, $P < 0.001$). According to the results of UDS and clinical data, 70 patients were diagnosed (73%) with overactive bladder (OAB). While DV was accompanied by OAB in 18 patients (18.7%), pure DV was diagnosed in 8 patients (8.3%).

Table 1 shows the relationship of VUR, UTI and renal damage with LUTD. The rate of VUR, UTI and renal damage in patients with OAB plus DV and pure DV was higher than in patients with OAB.

Table 1 The relationship between the pattern of LUTD and VUR, UTI and renal damage.

	OAB % ($n = 70$)	OAB + DV % ($n = 18$)	DV ($n = 8$) %
VUR ($n = 37$)	28.5 (20)	66.6 (12)	62.5 (5)
UTI ($n = 45$)	27 (19)	100 (18)	100 (8)
Renal damage ($n = 25$)	7 (5)	78 (14)	75 (6)

VUR was detected in 37 patients (38.5%), of whom 75.6% had unilateral and 24.3% had bilateral reflux. Non-dilating VUR was documented in 20 patients (54%), and 17 patients (46%) had dilating VUR. The rate of VUR in the girls (86.4%) was significantly higher than in the boys (13.5%) ($P < 0.05$).

UTI was detected in 45 patients (46.8%). All patients with OAB plus DV and pure DV had UTI (Table 1). The rate of VUR was significantly higher among the patients who had UTI (68% vs 32%, $P < 0.05$) (Table 2). Furthermore, VUR and UTI were documented in 31 patients, of whom 14 (45%) had non-dilating and 17 (55%) had dilating reflux (Table 3).

Renal scarring was detected in 25 patients (26%), of whom 78% had OAB plus DV and 75% DV only (Table 1). The presence of VUR among the patients with LUTD significantly increased the rate of renal damage (76% vs 24%) (Table 2). In addition, dilating reflux caused significantly greater renal damage on DMSA scan compared to non-dilating reflux (68.5% vs 31.5%, $P < 0.05$) (Table 3).

Twenty-four patients (25%) had constipation at their first visit. Also, 11 of them had encopresis. All patients were successfully treated by diet and medication.

Discussion

The factors affecting the presence of VUR, UTI and renal damage in children with idiopathic LUTD are still not understood completely. It has been revealed that LUTD may cause VUR and UTI, and may produce a urinary tract anatomy similar to that associated with neurogenic bladder abnormalities or obstruction [4,6,9,10].

Idiopathic LUTD represents a disturbance of the lower urinary tract dynamics affecting urine storage or emptying without neurological or anatomical abnormalities. OAB, which is the most common pattern in children with LUTD, is thought to be due to a delay in acquisition of cortical inhibition over uninhibited detrusor contractions in the course of achieving the mature voiding pattern of adulthood [11]. During bladder filling, these uninhibited detrusor contractions are recognized by the child as a sense of urgency, and the child responds with the pelvic floor contraction. Abnormal overactivity of the pelvic floor musculature during voiding, instead of a complete relaxation, results in interrupted micturation. Hence, DV that represents an abnormal voiding pattern as a consequence of a lack of coordination between the detrusor and external sphincter during voiding is commonly viewed as a learned response to a long-standing history of detrusor overactivity. In recent studies, the rate of OAB in children with LUTD was reported variously as 58% and 71%. It has been suggested that the rate of DV is lower than that of OAB [12,13]. In our series, while 73% of patients with LUTD had OAB, DV appeared in only 8.3% of patients. In addition, 18.7% of our patients had DV associated with OAB.

The earliest studies of LUTD mostly dealt with either OAB or DV. This is a somewhat artificial distinction, as the two conditions are often combined and sometimes difficult to separate. In patients with LUTD, uninhibited detrusor contractions and voluntary constriction of the sphincter, causing a functional obstruction, increase the intravesical pressure. Increased intravesical pressure can promote VUR through a possible marginal competence in the valve mechanism [9,14,17]. In the early 1980s, it was reported that a connection between OAB and VUR was mainly seen in girls after the age for bladder control [15,16]. Recent studies have shown that the prevalence of VUR among children with idiopathic LUTD is between 14% and 46% [12,13]. Our results revealed that VUR appears more frequently in girls, and overall 38.5% of our patients with LUTD had VUR. Although, some reports have emphasized bilateral reflux associated with LUTD [10,13], the rate of unilateral reflux was significantly higher in our series.

The causal connection between the pattern of the LUTD and reflux remains incompletely understood. It is hypothesized that increased intravesical pressure causes the development of reflux and/or perpetuates it in children with LUTD [10,17,18]. There is not sufficient reported data on the relationship between the type of LUTD and VUR. In a recent study, Ural et al. reported that the rate of VUR was similar among patients with OAB, OAB plus DV, and pure DV [13]. In contrast, in our series the rate of VUR in children with DV and OAB plus DV was significantly higher than in the OAB group. Although, detrusor pressure data obtained from UDS have not been included, we believe that the most important factor may be increased intravesical pressure during voiding.

Several authors have documented the relationship between OAB, DV and recurrent UTI. Recurrent UTI has been shown in many studies to be higher in VUR patients with bladder dysfunction than in those without such dysfunction [4–6,19]. It has been demonstrated that adequate management of LUTD not only decreases the rate of UTI but also increases resolution of the VUR [5,9,20]. Traditionally, recurrent UTI and pyelonephritis have been recognized as potential causes of permanent renal damage [21]. Current opinion is that VUR alone is not sufficient to cause UTI or renal damage. Holland et al. reported that girls with primary VUR followed up for 10 years, with no recurrent UTI, did not develop renal scars [22]. Linshaw showed that VUR does not threaten the kidney as long as UTI is promptly treated [23]. The results of these studies suggest that the association between VUR and UTI is necessary for renal damage to occur, mainly in situations of low detrusor pressure. However, VUR may predispose

Table 2 The relationship of VUR with UTI and renal damage.

	VUR(+) % ($n = 37$)	VUR(−) % ($n = 59$)	P
Female	86.4 (32)	66.1 (39)	NS
Male	13.5 (5)	33.8 (20)	$P < 0.05$
UTI	69 (31)	31 (14)	$P < 0.05$
Renal damage	76 (19)	24 (6)	$P < 0.05$

Table 3 The relationship between grade of reflux, and UTI and renal damage.

	Non-dilating VUR %	Dilating VUR %	*P*
UTI ($n = 31$)	45 (14)	55 (17)	NS
Renal damage ($n = 19$)	31.5 (6)	68.5 (13)	$P < 0.05$

invasion of the renal parenchyma by bacteria. It has been reported that bladder dysfunction is an important risk factor for VUR and renal damage [24]. In addition, current studies have showed that increased intravesical pressure associated with LUTD is a primary factor for inducing reflux and renal damage [13,17]. In patients who had UTI the presence of reflux increased the rate of renal damage [13]. In the present study, the rate of both UTI and renal damage in LUTD patients with associated VUR was significantly higher than in children without reflux. Moreover, the rate of renal damage in children with dilating VUR was higher than in those with non-dilating VUR.

Conclusions

In this series, OAB was the most common pattern of LUTD and could be associated with DV. OAB plus DV and pure DV were the main risk factors for VUR, UTI and renal damage. The presence of VUR in children with LUTD plays an important role with regard to UTI and renal damage. Moreover, dilating VUR is a major risk factor associated with renal damage.

Conflict of interest

None.

Funding

None.

References

[1] Koff SA, Jayanthi VR. Non-neurogenic lower urinary tract dysfunction. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. 8th ed. Philadelphia: Saunders; 2002. p. 2261—83.
[2] Dacher JN, Savoye-Collet C. Urinary tract infection and functional bladder sphincter disorders in children. Eur Radiol 2004;14:L101.
[3] Swerkersson S, Jodal U, Sixth R, Stokland E, Hasson S. Relationship among vesicoureteric reflux, urinary tract infection and renal damage in children. J Urol 2007;178:647.
[4] Snodgrass W. Relationship of voiding dysfunction to urinary tract infection and vesicoureteric reflux in children. Urology 1991;38:341—4.
[5] Snodgrass W. The impact of treated dysfunctional voiding on the nonsurgical management of vesicoureteric reflux. J Urol 1998;160:1823—5.
[6] Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol 1998;160:1019—22.
[7] Vega-P JM, Pascual LA. High-pressure bladder: an underlying factor mediating renal damage in the absence of reflux? BJU Int 2001;87:581—4.
[8] Neveus T, von Gontard A, Hoebeke P, Hjalmas K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006;176:314—24.
[9] Koff SA. Relationship between dysfunctional voiding and reflux. J Urol 1992;148:1703—7.
[10] Soygür T, Arıkan N, Yeşilli Ç, Göğüş O. Relationship among pediatric voiding dysfunction and vesicoureteral reflux and renal scars. Urology 1999;54:905—8.
[11] Franco I. Overactive bladder in children. Part 1: pathophysiology. J Urol 2007;178:761—8.
[12] Hoebeke P, Van Laecke E, Van Camp C, Raes A, Van De Walle J. One thousand video-urodynamics studies in children with non-neurogenic bladder sphincter dysfunction. BJU Int 2001;87:575—80.
[13] Ural Z, Ulman I, Avanoglu A. Bladder dynamics and vesicoureteric reflux: factors associated with idiopathic lower urinary tract dysfunction in children. J Urol 2008;179:1564—7.
[14] Sillen U. Bladder dysfunction and vesicoureteral reflux. Adv Urol 2008;815472:1—8.
[15] Taylor CM, Corkey JJ, White RHR. Micturition symptoms and unstable bladder activity in girls with primary vesicoureteric reflux. BJU 1982;54:494—8.
[16] Koff SA, Murtagh DS. The uninhibited bladder in children: effect of treatment on recurrence of urinary infection and on vesicoureteral reflux resolution. J Urol 1983;130:1138—41.
[17] Acar B, Arıkan FI, Germiyanoglu C, Dallar Y. Influence of high bladder pressure on vesicoureteral reflux and its resolution. Urol Int 2009;82:77—80.
[18] Chandra M, Maddix H. Urodynamic dysfunction in infants with vesicoureteral reflux. J Pediatr 2000;136:754—9.
[19] Sjöström S, Sillen U, Bachelard M, Hansson S, Stockland E. Spontaneous resolution of high grade infantile vesicoureteral reflux. J Urol 2004;172:694—8.
[20] Kibar Y, Ors O, Demir E, Kalman S, Sakallıoglu O, Dayanç M. Results of biofeedback treatment on reflux resolution rates in children. Urology 2007;70:563—6.
[21] Winberg J. Progressive renal damage from infection with or without reflux. J Urol 1992;148:1733—4.
[22] Holland N, Jackson E, Kazee M, Conrad GR, Ryo UY. Relation of urinary tract infection and vesicoureteral reflux to scars: follow up in 38 patients. J Pediatr 1990;116:S65—71.
[23] Linshaw MA. Asymptomatic bacteriuria and vesicoureteral reflux in children. Kidney Int 1996;50:312—29.
[24] Naseer SR, Steinhardt GF. New renal scars in children with urinary tract infection, vesicoureteral reflux and voiding dysfunction: a prospective evaluation. J Urol 1997;158:566—8.