Bladder Dynamics and Vesicoureteral Reflux: Factors Associated With Idiopathic Lower Urinary Tract Dysfunction in Children

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Purpose: The objective of this study was to determine the clinical, demographic, urodynamic and prognostic characteristics related to vesicoureteral reflux among patients with idiopathic lower urinary tract dysfunction.

Materials and Methods: We retrospectively reviewed the records of 348 children with idiopathic detrusor overactivity or dysfunctional voiding who had been examined for vesicoureteral reflux between 1995 and 2005 at a university hospital. Demographic, clinical and urodynamic parameters were compared between groups according to the presence, grade, laterality and resolution of vesicoureteral reflux.

Results: Among the 348 patients 8 infants were excluded from statistical analysis and are discussed separately. Among the 340 remaining patients 1 year and older vesicoureteral reflux was documented in 155 (46%), of whom 32% had bilateral reflux. Of the overall cases 60% were grade III or higher. Mean age in the refluxing group (6.5 ± 2.8 years) was significantly lower than in the nonrefluxing group (7.6 ± 2.5 years, $p < 0.001$). Continent children presented with a significantly higher rate of vesicoureteral reflux compared to incontinent children (74% vs 42%, $p < 0.001$). Among the patients who had urinary tract infection the presence of reflux increased the rate of renal cortical abnormalities (45% vs 17%, $p < 0.001$). However, among patients who were free of urinary tract infection the presence of reflux was not associated with cortical abnormalities (25% vs 24%, $p > 0.05$). Median maximum filling pressure was higher in the refluxing group compared to the nonrefluxing group (40.0 vs 34.0 cm H_2O, $p < 0.001$). Detrusor overactivity and dysfunctional voiding showed similar rates for development of vesicoureteral reflux. Reflux was resolved with medical treatment in 40% of the patients. The resolution rate was significantly higher in children with nondilating reflux and initial lower median cystometric bladder capacity.

Conclusions: Vesicoureteral reflux is associated with daytime incontinence, urinary tract infection, younger age and renal cortical abnormalities among patients with idiopathic lower urinary tract dysfunction. Increased intravesical pressures seem to be the primary factor for inducing reflux in idiopathic lower urinary tract dysfunction. Initial bladder capacity predicts the resolution of reflux.

Key Words: urinary bladder, overactive; urination disorders; urinary incontinence; vesicoureteral reflux

Dynamic changes can affect ureterotrigonal structure and result in VUR. The association between nonneuropathic or nonanatomical abnormalities of lower urinary tract function and VUR in infants and children has long been reported.[1] Increased intravesical pressures cause a spectrum of intravesical anatomical distortions that predispose to VUR.[2] Some clinicians suspect that reflux is a secondary phenomenon, appearing as a result of detrusor overactivity rather than as a primary ureterovesical junction abnormality.[3] The bulk of the literature consists of research that describes the rate and characteristics of ILUTD through investigating VUR case series, with few studies providing urodynamic results. To our knowledge only 1 study has assessed the rate and characteristics of VUR among patients with ILUTD.[4] The objective of this study was to determine the clinical, demographic, urodynamic and prognostic characteristics related to VUR among patients diagnosed with ILUTD.

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Approval of institutional research ethics committee was not required for this retrospective study. Ethics concerns of the Helsinki Declaration were followed.

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MATERIALS AND METHODS

Study Population

We retrospectively reviewed the records of patients who had been diagnosed with idiopathic OAD or DV between 1995 and 2005 at a referral center for pediatric urology. The study population consisted of 348 children who underwent complete urodynamic investigation for ILUTD, in whom VUR was examined via VCUG. The patient population consisted of 340 children and 8 infants (younger than 12 months). The findings related to the 8 infants were excluded from statistical comparisons and are discussed separately. The International Reflux Study Classification was used to grade reflux on VCUG. A DMSA renal scan was performed in 276 of the patients to assess renal cortical abnormalities. Hypoactive areas, contour defects and low differential renal function (less than 45%) were defined as renal cortical abnormalities.

The presence, laterality, dilatation and resolution of VUR on VCUG were examined in the study group. The grade and resolution rate of VUR were related to the patient, not the

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ureter. Patients with bilateral reflux were categorized by the higher reflux grade. Grades I and II were defined as nondilating and grades III, IV and V as dilating reflux. The distribution of demographic, clinical and urodynamic parameters was compared between the groups.

Complete conventional urodynamic studies were performed in all patients while they were awake and seated. We performed at least 3 voiding cycles and never drew conclusions from the first cycle. Urodynamic testing methods, definitions and units suggested by the International Children's Continence Society were used.[5] The mean value of 3 consecutive cystometric bladder capacities was recorded as the percent of the expected cystometric bladder capacity for age.[6] 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 DV.[5] Medical management of ILUTD was based on explanation and elucidation of the voiding cycle, correction of faulty voiding habits, instruction about how and when to void, prophylactic antibiotics for VUR, treatment of constipation and anticholinergics for overactive contractions.

Data on 73 patients (21%) who were followed regularly for at least 1 year were analyzed for the prognostic part of the survey. During this part of the analysis 2 groups were differentiated based on the presence of resolution. The detection of 1 negative VCUG 1 year after diagnosis in an asymptomatic patient without UTI was considered resolution of reflux. Patients with persistent or reduced grade reflux and those who received antireflux intervention were defined as the nonresolution group. Antireflux intervention was reserved for breakthrough UTI, detection of new renal scarring on prophylaxis and lack of compliance.

Selection Criteria for Urodynamic Investigation and Voiding Cystourethrography

Patients with daytime incontinence, urgency and increased voiding frequency were assessed with complete urological and neurological examinations, urinalysis and ultrasonography. If there was no history of UTI or ultrasonographic abnormality, cases were described as OAB. Patients with OAB had received explanation and elucidation of the voiding cycle, correction of faulty voiding habits, instructions about how and when to void, treatment of concomitant constipation and empirical anticholinergics. The selection criteria for urodynamic study included a history of UTI, ultrasonographic abnormalities, presence of VUR, hesitancy, straining, weak stream or intermittency and resistance to therapy for OAB. A history of UTI was the only indication for VCUG.

Inclusion and Exclusion Criteria

Neurologically normal children without any urogenital anatomical problem except VUR were included in the study. Those with other urogenital anatomical conditions (eg posterior urethral valves, ureterocele, meatal stenosis, labial synechiae) were excluded from the study. Additional exclusion criteria were systemic disorders, hypercalciuria and anorectal malformation. Patients with ILUTD represent a heterogeneous group with filling and voiding abnormalities. By excluding underactive detrusor and other rare forms of ILUTD (Hinman syndrome, giggle incontinence), a relatively homogeneous study population was constructed for statistical analysis and discussion. Children with mental delay were also excluded from the study.

Statistical Analysis

Data were analyzed in SPSS® version 10.0. Categorical variables were compared with the chi-square test. Student's t test was used for comparison of continuous variables when the data followed a normal distribution. Mann-Whitney U test was used for comparison of continuous variables when the data did not follow a normal distribution. A p value of less than 0.05 was considered statistically significant. Definitions conform to the standards recommended by the International Children's Continence Society, except where specifically noted.[5]

RESULTS

There were a total of 348 patients in the series, of whom 8 were infants (younger than 12 months). All findings are presented for the 340 patients 1 year or older, unless otherwise specified. Among the 340 patients 273 (80%) were female and 67 (20%) were male. Patient age ranged from 1.5 to 15.0 years, with a mean ± SD of 7.1 ± 2.7. A total of 101 patients (30%) were 5 years or younger, and 239 (70%) were older than 5 years at admission to the study. There were 241 patients (71%) diagnosed with idiopathic OAD. Only 22 patients in the series (6%) demonstrated pure DV. Idiopathic DV was accompanied by OAD in 79 patients (22%). Among the sample there were 13 patients with contralateral VUR detected following previous surgical intervention, and 1 patient with failure after previous antireflux surgery.

Vesicoureteral reflux was documented in 155 patients (46%), of whom 32% had bilateral reflux. Mean age at admission in the refluxing group (6.5 ± 2.8 years) was significantly lower than in the nonrefluxing group (7.6 ± 2.5 years, $p < 0.001$). Of the cases 60% had dilating reflux. Reflux rates were reported as 19%, 22%, 33%, 16% and 9% for grades I to V, respectively. Mean age in the bilateral reflux group was similar to the unilateral reflux group (6.2 ± 2.8 years vs 6.8 ± 2.8 years).

When boys and girls were compared the rate of girls with a UTI (88%) was significantly higher than boys (62%, $p < 0.001$). There were no other significant differences related to the sex of the child in the series. The impact of age with features of reflux and UTI by gender in the survey is presented in table 1. Among the patients who had UTI the presence of VUR increased the rate of renal cortical abnormalities (45% vs 17%, $p < 0.001$). However, among patients who were free of UTI the presence of VUR was not associated with cortical changes (25% vs 24%, $p > 0.05$). The median (25th and 75th percentiles) maximal detrusor pressure during filling was 40.0 cm H_2O (range 25.0 to 60.0) in the refluxing group, compared to 34.0 cm H_2O (20.0 to 45.0) in the nonrefluxing group ($p < 0.001$).

Dilating reflux caused significantly higher renal cortical abnormalities on DMSA scan compared to nondilating reflux (48% vs 28%, $p = 0.03$). The rate and laterality of VUR were similar among patients with OAD, OAD plus DV and pure DV. The features related to VUR are presented in table 2.

The records of 73 patients were analyzed for the prognostic part of the survey. The median (25th and 75th percentiles) followup time was 24 months (range 18 to 34). Reflux

TABLE 1. *Impact of age on features of reflux and urinary tract infection by gender*

	No. VUR (%)			
	Overall	Bilat	Dilating	No. UTI (%)
Boys:				
1–5 Yrs	7 (47)	1 (14)	6 (86)	13 (87)
Older than 5 yrs	23 (44)	9 (40)	14 (61)	26 (54)
p Value	Not significant	Not significant	Not significant	0.033
Girls:				
1–5 Yrs	55 (64)	18 (35)	28 (56)	80 (96)
Older than 5 yrs	70 (37)	20 (29)	38 (57)	157 (85)
p Value	<0.001	Not significant	Not significant	0.005

resolved with medical management in 40% of the cases. Overall resolution rates were 58%, 71%, 26% and 21% for reflux grades I to IV, respectively. Resolution with medical treatment was achieved in 66% of the patients with nondilating reflux and 21% of those with dilating reflux ($p < 0.001$). The resolution rate was 26% for bilateral reflux and 48% for unilateral reflux ($p = 0.066$).

Median (25th and 75th percentiles) cystometric bladder capacity as the percent of the expected cystometric bladder capacity for age was 64% (range 33% to 91%) in the resolution group compared to 80% (51% to 100%) in the nonresolution group ($p = 0.037$). The resolution rate was higher with high filling pressures at admission, although the difference was not statistically significant. Median maximal detrusor pressure during filling was 60.0 cm H_2O (range 25.0 to 90.0) in the resolution group, compared to 40.0 cm H_2O (21.0 to 60.0) in the nonresolution group ($p = 0.086$). Neither age nor sex had a significant association with the rate of reflux resolution.

All 8 infants studied were male. Seven of these patients presented with bilateral dilating VUR and breakthrough UTI, and 1 presented with breakthrough UTI without VUR. Seven of the infants underwent DMSA scan. Renal cortical abnormalities were noted in 6 patients. Urodynamic investigation revealed phasic detrusor overactivity during filling and interrupted voiding in 2 of the infants. Six infants had OAD, while 2 exhibited terminal detrusor overactivity.[7] Perineal electromyography was not interpretable in 2 patients.

DISCUSSION

The relationship between lower urinary tract function and VUR in children is unclear. Since normal bladder dynamics and the neural maturation process over bladder control is not well documented in infants, ILUTD diagnosis remains somewhat controversial among infants. The developing child (younger than 1 year) tends to have coordinated bladder activity, with voiding occurring about once hourly.[8] Yeung et al reported that in comparison with the "normal" controls, 57% of the infants with reflux showed abnormal urodynamic patterns not found in any of the "controls."[9] High grade VUR has been suggested to be caused by congenital malformation, which might originate in a urethral bud anomaly and might also explain ILUTD.[10] The 8 male infants in our series might represent congenital ILUTD rather than transitional developmental immaturity of the lower urinary tract.

TABLE 2. *Demographic and clinical characteristics of reflux in idiopathic lower urinary tract dysfunction*

	% Pos VUR	% Neg VUR	p Value
Sex:			
M	45	55	Not significant
F	46	54	
UTI:			
Pos	49	51	0.002
Neg	26	74	
Holding maneuvers:			
Yes	36	64	Not significant
No	48	52	
Urgency:			
Present	37	63	0.005
Absent	52	48	
Incontinence:			
Present	42	58	<0.001
Absent	74	26	

As we anticipated, the mean age in the refluxing group was significantly lower than in the nonrefluxing group. However, in this study it was determined that the rate of VUR was higher for patients 5 years and younger compared to the older ones for both sexes, although the difference was not statistically significant for boys, probably due to the small sample size. We did not detect the bimodal pattern of VUR regarding age between the sexes.[11] While reflux alone does not seem to increase the rate of renal cortical abnormalities, in this series reflux caused significantly higher renal cortical abnormalities in patients with UTI, which supports the concept that VUR might facilitate renal involvement once bacteriuria have been established in the bladder.

It is hypothesized that increased filling pressure might perpetuate reflux in ILUTD.[3] It was noted that the voluntary constriction of the sphincter, in an attempt to keep from wetting during overactive detrusor contractions, causes a functional urinary obstruction with the increased intravesical pressure. In our study the refluxing group demonstrated significantly higher pressures during the filling phase but reported significantly less urgency and incontinence. The individual sense of overactive detrusor contractions and the response to overactive contractions are individually, socially and probably genetically determined. Some children overcome overactive detrusor contractions by voluntary pelvic floor contraction, which helps them to stay dry and probably extends the portion of the filling phase where bladder is exposed to increased filling pressures. This is not the case for other children who do not (cannot) try to resist overactive detrusor contractions and, thus, experience incontinence, releasing intravesical pressure before reaching a critical level.

Koff noted that filling and voiding dysfunctions share a common urodynamic mechanism in that they both produce functional urinary obstruction, which is a major contributing factor in induction of VUR.[3] Our results revealed that 77% of DV was accompanied by overactive

detrusor contractions in the filling phase. When we explored the VUR rate distribution between the 3 groups (OAD, pure DV, and OAD plus DV) we did not detect any significant difference. Laterality of the reflux and renal cortical abnormalities did not appear to be related to the type of ILUTD in our series, similar to other series in the literature.[4,12] Since the rate of VUR was similar among patients with OAD, OAD plus DV, and pure DV, we can conclude that detrusor overactivity and sphincter overactivity cause similar intravesical anatomical distortions to produce reflux in patients with ILUTD.

In contrast to our preference, some series in the literature include underactive detrusor and other severe forms of ILUTD (eg Hinman syndrome). This preference may have an impact on our results, in that DV was not associated with significantly higher rates of bilateral reflux or renal damage in patients with VUR. We did not perform VCUG or urodynamic study in every patient thought to have ILUTD. As we selected our patients for urodynamic investigation and VCUG, as in most of the series in the literature, our results may have been affected by selection bias caused by exclusion of some patients with a history of isolated pure filling phase dysfunction from the study. Finally, since these data are from a tertiary referral center, they probably comprise more severe cases. Therefore, it may be impossible to apply these results to the general population.

The most important clinical factor for resolution was VUR grade, which greatly influences treatment and followup. A higher nonresolution rate in dilating reflux can be explained by the irreversible derangement of the ureterovesical junction. Initial lower median cystometric bladder capacity was a favorable prognostic factor. It is known that treatment of overactive detrusor contractions with anticholinergics increases the threshold for overactive detrusor contractions, enlarges functional bladder capacity, and, thus, reduces the intravesical pressure and improves reflux resolution. Our data also suggest that elimination of overactive detrusor contractions, and, consequently, improvement in bladder capacity may be a significant contributing factor for the resolution of VUR in patients with ILUTD. Resolution seems to be the result of improved bladder storage and voiding dynamics in our series, as stated by others.[12] Based on the available data, it is clear that treatment of ILUTD is mandatory before any surgical intervention for reflux, because of the possibility of reflux resolution and the risk of reflux recurrence.

Several limitations exist in this retrospective study. There is no control group of children with reflux without ILUTD. Therefore, it is difficult to draw any conclusions regarding whether VUR behaves differently when seen together with ILUTD. As a result, we were able to make only descriptive conclusions in a selected study group. Our sample size for the prognostic part of the survey did not permit complete evaluation of all possible factors related to reflux resolution.

CONCLUSIONS

Our data indicate high filling pressure as the significant determining factor in the pathophysiology of VUR regardless of whether ILUTD induces reflux by destroying the susceptible antireflux mechanism or by association with a congenital malformation of the ureters. Much can be said for the association of ILUTD and VUR in infants after studies to answer whether ILUTD and VUR are mutually sustained during the prenatal period.

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Abbreviations and Acronyms

DMSA	=	^{99m}technetium dimercapto-succinic acid
DV	=	dysfunctional voiding
ILUTD	=	idiopathic lower urinary tract dysfunction
OAB	=	overactive bladder
OAD	=	detrusor overactivity
UTI	=	urinary tract infection
VCUG	=	voiding cystourethrography
VUR	=	vesicoureteral reflux

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