
Predictive Factors for Contralateral Reflux in Patients With Conservatively Treated Unilateral Vesicoureteral Reflux

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Purpose: We evaluated the rate of new contralateral reflux in children with conservatively treated vesicoureteral reflux, and identified predictive factors that could influence the appearance of contralateral reflux after a diagnosis of unilateral reflux on the first voiding cystourethrogram.

Materials and Methods: We retrospectively evaluated 167 children who had been diagnosed with unilateral vesicoureteral reflux on the first voiding cystourethrogram. Patients with bilateral or secondary vesicoureteral reflux and those who had undergone only 1 voiding cystourethrography were excluded from the study. A total of 134 girls and 33 boys were analyzed. Average patient age was 55 months (range 2 to 169). All children had undergone at least 2 voiding cystourethrograms. A total of 84 patients underwent 3 voiding cystourethrograms, 35 underwent 4, 18 underwent 5, 9 underwent 6 and 3 underwent 7.

Results: New contralateral reflux was evident on subsequent voiding cystourethrography in 35 patients (21%). Analysis of the presence of new contralateral reflux according to gender, reflux grade, age, side of reflux and bladder function (with or without lower urinary tract dysfunction) revealed that only medium or high grade reflux was a risk factor for new contralateral reflux. In 98 children (59%) vesicoureteral reflux resolved spontaneously. Of these patients 13 had new contralateral reflux and 85 did not ($p = 0.017$).

Conclusions: We identified a 21% incidence of new contralateral reflux in patients with unilateral reflux after the first voiding cystourethrography who were treated conservatively. The main risk factor for contralateral reflux was the presence of medium or high grade reflux. Patients with new contralateral reflux had a lower rate of cure than those without development of contralateral reflux.

Key Words: vesico-ureteral reflux, urodynamics, urinary bladder, ureter

New contralateral reflux occurs in 10% to 20% of patients treated with endoscopic injection or ureteral reimplantation.¹⁻³ Various mechanisms are imputed as causative or facilitative of NCR, including the end of the “pop-off” mechanism and the distortion of the trigone. However, some cases of NCR may simply represent previous VUR that went undiagnosed because of the inaccuracy of VCUG. New contralateral vesicoureteral reflux has been reported in patients treated conservatively for unilateral reflux, at a rate of 33% in 143 children with unilateral reflux.^{4,5} It is important to identify bilateral vesicoureteral reflux in the prognosis and treatment of these children. Of primary concern is that vesicoureteral reflux presents the possibility of renal scarring, and that the presence of NCR may increase the chance of lesions in the kidney. Also, the rate of spontaneous resolution of bilateral high grade reflux is lower than in unilateral cases.²

Despite the high rate of NCR in cases of conservatively managed VUR,⁵ there are no predictive factors for contralateral reflux. As proposed by some authors, potential predic-

tive factors could indicate which patients would benefit from a bilateral injection in the presence of unilateral reflux.^{3,6} The objective of this study was to evaluate the rate of NCR in children with conservatively treated VUR, and to identify predictive factors that could influence the appearance of contralateral reflux in patients diagnosed with unilateral reflux based on the first VCUG.

MATERIALS AND METHODS

We retrospectively evaluated 167 children who had been diagnosed with unilateral VUR on a first VCUG between 1986 and 2004. These cases were collected from our vesicoureteral reflux database. We excluded cases with urological abnormalities, such as posterior urethral valves, neurogenic bladder, ureterocele and ectopic ureters, from the analysis. Patients with bilateral VUR as well as those who had undergone only 1 VCUG were also excluded.

A total of 134 girls and 33 boys were analyzed. Average patient age was 55 months (range 2 to 169). A total of 103 patients had reflux on the left side and 64 on the right side. In 14 cases reflux was diagnosed by scintigraphy. In these cases VUR grading was not possible. A total of 21 patients had grade I, 70 had grade II, 48 had grade III, 13 had grade IV and 1 had grade V reflux. Grade III reflux was defined as “medium grade,” and grade IV and V as “high grade.”

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There was a duplex renal system on the VUR side in 5 patients. In all of these patients reflux was to the lower pole (grade II in 3, grade III in 2). Among 76 children older than 4 years LUTD was detected in 24. A total of 148 patients had a history of urinary tract infection.

Voiding cystourethrograms were performed with fluoroscopy and VUR was graded by an experienced pediatric urologist. Another cycling was performed only if the first was unsatisfactory. No sedation was used. All children underwent at least 2 VCUGs. A total of 84 patients underwent 3 VCUGs, 35 underwent 4, 18 underwent 5, 9 underwent 6 and 3 underwent 7. All patients were maintained on antibiotic prophylaxis. Indications for surgery included urinary tract infection despite antibiotics, and persistent reflux accompanying development of the child.

Student's t test was used to compare continuous variables between the groups. The chi-square or Fisher test was performed to compare qualitative variables.

RESULTS

Among 167 patients NCR was evident in 33 (21%). Average number of VCUGs and scintigrams performed was 2.6 ± 1 in patients without NCR and 3.5 ± 1.4 in patients with NCR ($p < 0.001$). Table 1 outlines the presence of NCR according to gender, reflux grade, age, side of reflux and bladder function (with or without LUTD). Of all these parameters only medium or high grade reflux was a risk factor for NCR. There was no significant difference between grade III and grade IV to V reflux. Of patients with low, medium and high grade VUR 13%, 31% and 43%, respectively, presented with NCR.

In 98 children (59%) VUR resolved spontaneously (table 2). Of these patients 13 had NCR and 85 did not ($p = 0.017$). Average number of episodes of symptomatic urinary tract infection confirmed by culture was 2.3 ± 1.7 in patients with NCR and 2.6 ± 1.7 in patients without NCR ($p = 0.34$). A total of 30 patients had NCR diagnosed on the second VCUG, 2 on the third and 1 on the fourth. New contralateral reflux was grade I in 4 of these children, grade II in 18, grade III in 9 and grade IV in 1. One child was assessed by radioisotopic cystography and could not be evaluated for

TABLE 1. Correlation between presence of NCR and patient gender, age, side of reflux, reflux grade and lower urinary tract dysfunction

	No. NCR	No. No NCR	p Value
Gender:			
M	2	31	0.18
F	31	103	
Side:			
Lt	18	85	0.43
Rt	15	49	
Age:			
Younger than 2 yrs	7	34	0.82
Older than 2 yrs	26	100	
Reflux grade:			
I-II	12	79	*
III	15	33	
IV-V	6	8	
LUTD:			
Present	4	20	0.945
Absent	9	43	

* Grade I to II vs grade III reflux $p = 0.10$, grade I to II vs grade IV to V reflux $p = 0.14$ and grade III vs grade IV to V reflux $p = 0.52$.

TABLE 2. Rate of spontaneous resolution in patients with vesicoureteral reflux with and without NCR

	Spontaneous Resolution		p Value
	No	Yes	
NCR	20	13	0.0172*
No NCR	49	85	

* Odds ratio 2.669 (95% CI 1.22-5.88).

VUR grading. Seven patients with NCR and 12 without NCR had undergone antireflux surgery.

DISCUSSION

Voiding cystourethrogram is most commonly the first examination requested for a VUR diagnosis. We found that 21% of our patients tested positive for NCR after the first VCUG. This rate of NCR is lower than the 33% rate published by Sparr et al.⁵

Our data also demonstrated that only reflux grade correlated with NCR appearance. With regard to medium and high grade reflux, 31% and 43% of patients, respectively, presented with NCR. These data raise prognostic concerns and may influence the treatment decision. High grade bilateral VUR has a lower rate of spontaneous resolution than its unilateral counterpart.² Other parameters such as age, gender, urinary tract infection, side of reflux and presence of LUTD were not predictors of NCR. Our data also showed that NCR appeared on the second VCUG in 91% of the cases. In other words the probability of NCR after the second VCUG is low.

The rate of spontaneous resolution of reflux (39%) was lower in the group with NCR. Patients with NCR underwent more VCUGs than those without NCR. Unlike Sparr et al,⁵ we considered followup as the last VCUG instead the last clinic visit. The higher number of VCUGs in the NCR group probably reflects the lower rate of spontaneous reflux resolution in this group and the longer followup of these patients. Our study revealed that 33% of the NCR group fell in the medium and high grade categories (9 patients with grade III and 1 with grade IV reflux). This finding is not in accordance with the 9% rate of grade III reflux reported by Sparr et al.⁵

In our study VCUG was performed by an experienced pediatric urologist, and reflux was graded by a pediatric urologist. Craig et al reported a high concordance between pediatric urologists and urologists in VCUG reflux grading.⁷ However, as many other authors agree, there may be a discrepancy between one VCUG and another.¹ In cases of a first negative VCUG for reflux VUR can be found on the second examination at a rate of 20% to 30%.^{8,9} Jequier and Jequier observed that the rate of VUR and its grade varied from one filling to another in 22 of 177 patients (12%) with a second cycle and in 6 of 30 (20%) with a third cycle of VCUG.¹⁰ These findings were confirmed by other studies.¹¹

We believe that NCR after a first VCUG that demonstrates unilateral reflux can be a result of a loss of sensitivity of the examination. We hypothesize that unilateral medium and high grade reflux might reduce the pressure into the bladder during the filling and emptying phases. This mechanism may accentuate the loss of the VCUG capacity to

diagnose reflux on the contralateral side, mainly in cases of high grade reflux.

Currently, many cases of VUR are managed by endoscopic injection after the first VCUG. Our data led us to the hypothesis that unilateral endoscopic injection should be performed only after a second VCUG, because around 90% of our cases were detected on the second examination. A study by Elmore et al evaluated the rate of contralateral reflux in 126 children who had undergone endoscopic injection for unilateral VUR.⁶ They reported that NCR was detected in 13.5% of the children. Of these patients 40.5% had the injection performed after the first VCUG. Therefore, we believe that some of these children had bilateral reflux and would benefit from treatment addressed to both ureters.

Recognizing predictive factors for NCR would aid in evaluation of the prognosis of patients with reflux, as well as facilitate the decision concerning which patients would benefit from bilateral endoscopic injection, even in unilateral reflux. Until the evolution of NCR is better understood this specific group of patients, ie those with medium and high grade reflux and only a single VCUG evaluation, should not be submitted to unilateral endoscopic injection after the first VCUG. New contralateral reflux developed in approximately a third of our patients, which suggests the necessity for the physician to discuss with the family the possibility of bilateral injection or performance of another confirmatory VCUG.

CONCLUSIONS

We observed a 21% incidence of contralateral VUR in patients with unilateral reflux after a first VCUG who were treated conservatively. The main risk factor for contralateral reflux was the presence of higher grade reflux. Patients with new contralateral reflux had a lower rate of cure than those who did not have contralateral reflux.

Abbreviations and Acronyms

LUTD	=	lower urinary tract dysfunction
NCR	=	new contralateral reflux
VCUG	=	voiding cystourethrogram
VUR	=	vesicoureteral reflux

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EDITORIAL COMMENT

The authors report that in patients with unilateral medium and high grade reflux the finding of NCR on followup VCUG is relatively common (33%). They warn against treating these patients based on the initial VCUG, and recommend either waiting for a second VCUG before treating or proceeding with bilateral endoscopic treatment. They also found that patients with NCR are less likely to have spontaneous resolution of the reflux. They believe that the undetected contralateral reflux is most likely initially missed because of variability in sensitivity of the VCUG.

Although the authors did not find LUTD to be a risk factor in the pathophysiology of NCR, I still have a sense that undiagnosed LUTD has a significant role in many of these cases, and could also explain why children with NCR have a lower rate of spontaneous resolution than those who do not have NCR. These patients should be carefully screened for signs and symptoms of LUTD, and treated if appropriate.

I am curious about the fate of the NCR itself. Among the 26 unoperated patients with NCR, what was the spontaneous resolution rate by grade on subsequent VCUGs?

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