

Heavy Scarring in the Unilateral Refluxing Kidney May Sign of Contralateral Reflux After Reimplantation

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What's known on the subject? and What does the study add?

The stone-kidney index was described as a straightforward method for predicting the success of pediatric percutaneous nephrolithotomy. In this study, we examined the stone-kidney index in pediatric retrograde intrarenal surgery for the first time to the best of our knowledge. The identified threshold value for a successful outcome was 1.96.

Abstract

Objective: The aim of this study was to investigate the role of heavy ipsilateral scarring in the development of the contralateral reflux after unilateral reimplantation.

Materials and Methods: The study included 43 patients (24 male, 19 female) who had undergone unilateral reimplantation. Heavy scarring was defined as the presence of multiple central scars on renal scan and differential function of less than 30% with diffuse parenchymal damage. Postoperative voiding cystourethrography was performed to evaluate febrile urinary tract infection or hydronephrosis during follow-up. The development of the contralateral reflux was compared based on the type of reimplantation, age, preoperative renal scar status, and reflux grade.

Results: Contralateral reflux developed in 6 children. No significant relationship was found between the pre-operative grade, type of reimplantation, and incidence of the contralateral reflux. However, *de novo* contralateral reflux was significantly higher in children with heavy scarring on the ipsilateral kidney. Among the five children with heavy kidney scarring and aged 4 years or younger, contralateral reflux was found in three children. Reflux was resolved within 24.6±12.2 months on average although one child recovered with Dx/HA implantation.

Conclusion: We found that the presence of heavy scarring in the ipsilateral kidney may play a role in the prediction of contralateral reflux development.

Keywords: Child-preschool, renal scarring, vesicoureteral reflux

Introduction

The ureteroneocystostomy (UNC) procedure is currently the most effective treatment for vesicoureteral reflux (VUR) in children, with a high success rate. However, the literature reports a contralateral reflux rate of 5.6–19% after unilateral UNC, with most cases showing spontaneous resolution during follow-up (1–4).

With the high success rate and the reported spontaneous resolution of contralateral reflux during follow-up, asymptomatic children undergoing the UNC procedure are not routinely recommended to undergo control voiding cystourethrography (VCUG). However, in children who have experienced febrile urinary tract infections, performing a follow-up VCUG is important to identify those at risk of developing scar tissue.

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An increased incidence of contralateral reflux in cases of multicystic dysplastic kidney may suggest a relationship between renal dysplasia and contralateral reflux (5). The presence of heavy scarring tissue suggests that renal dysplasia is related to the histological composition of the distal ureter, which can be related to the morphological and functional integrity of the ureteral-trigonal unit (6,7). Furthermore, while heavy renal damage indicates congenital involvement with higher degree reflux, it may also affect the contralateral orifice in relation to developmental deterioration or bladder dysfunction (8).

The objective of this study was to examine the factors that influence the development of *de novo* contralateral reflux following unilateral UNC and to investigate the potential association between heavy scarring indicative of renal dysplasia and contralateral reflux.

Materials and Methods

Fifty-eight patients who had unilateral UNC in the Hacettepe University Pediatric Urology Section with unilateral reflux on the VCUG between May 2001 and January 2008 were retrospectively investigated in their postoperative control visits.

A retrospective analysis was conducted on 58 patients who underwent unilateral UNC at the Hacettepe University Department of Urology Pediatric Urology section for a unilateral reflux on VCUG between May 2001 and January 2008. The Clinical Research Ethics Committee of The Bursa Uludağ University approved the study (approval number: 2023-2/18).

Patients who underwent ureteral reimplantation for obstruction, had associated neurological disorders, contralateral renal agenesis, undergone contralateral nephrectomy, or previously undergone DxHA implantation in the contralateral orifice, as well as those for whom preoperative renal scan could not be obtained, were excluded from the study. One patient who had undergone Boari flap and psoas hitch for ectopic ureter had recurrent bilateral reflux and another patient had recurrent ipsilateral reflux, both of whom were also excluded from the study. A total of 43 patients remained in the study group.

All children had a unilateral reflux at the time of the operation. Duplicated collecting systems were in 2 patients, Hutch diverticulum in 2 patients, and ectopic ureter with duplicated collecting system in 1 patient. Nineteen children had grade 3 reflux, 15 had grade 4 reflux, and 9 had grade 5 reflux before undergoing UNC.

The preoperative evaluation consisted of at least one VCUG, urinary ultrasound, urinalysis, urinary culture, and dimercaptosuccinic acid (DMSA) renal scintigraphy. The presence of multiple central scars on renal scintigraphy with global renal function less than 30% and diffuse parenchymal damage was

accepted as heavy scarring. All children underwent a lower urinary tract dysfunction evaluation after toilet training. Of these, six children were found to have bladder dysfunction, and all received treatment before surgery. Five patients underwent DxHA implantation in the same orifice before UNC.

UNC was performed intravesically using the Cohen technique in 28 children, while extravesically using the Lich Gregoir technique in 15 children.

Prophylactic antibiotics were administered for one month in the postoperative period. Urinalysis was performed monthly for the first three months and then quarterly for the first year. Urinary ultrasound was performed at the end of the first and third months and then at the end of the first year. VCUG or video urodynamics was performed only for patients who developed urinary tract infection and/or hydronephrosis during the follow-up period. Patients with postoperative reflux were followed up with VCUG. The complete resolution of VUR in the ipsilateral system following unilateral UNC was considered a success.

Statistical Analysis

Statistical analysis was performed using the SPSS version 20 software (SPSS, Inc. Chicago, Ill, USA). The Shapiro-Wilk test was used to test the normality of variables. The variables are presented as mean \pm standard deviation for normally distributed data and as median (minimum–maximum) for non-normally distributed data. Number and percentage were used for nominal data. Mann-Whitney U test was used for non-normally distributed variables, while Fisher's Exact test was used for nominal variables, and a *p* less than 0.05 was considered significant.

Results

Twenty-four of the children included in the study were boys and 19 were girls, while the mean age was 5.52 ± 3.22 years. The urethral catheter was removed on average after 3.26 ± 0.83 days. The resolution rate of reflux after UNC was 95.3% for the ipsilateral unit. During the follow-up period, 16 children underwent VCUG and 2 underwent video urodynamics. Contralateral reflux was found in 6 patients with *de novo* reflux being grade 1 in one child, grade 2 in two children, and grade 3 in three children. No recurring reflux was observed in children with bladder dysfunction. There was no significant difference in *de novo* contralateral reflux between genders.

No significant relationship was found between the preoperative grade and contralateral kidney reflux (*p*=0.7) (Table 1). The rates of contralateral reflux were similar for both intravesical and extravesical UNC procedures at 14.3% and 13.3%, respectively, and this difference was not statistically significant (*p*=1) (Table 1).

Table 1. Comparison of patient characteristics between groups

		No contralateral reflux	Contralateral reflux +	p
Age*		6 (1-13)	3.75 (1-7)	0.312
Gender (girl/boy)		16/21	3/3	1
UNC type (Int/ext)		24/13	4/2	1
Ipsilateral reflux grade	3	17 (89.5%)	2 (10.5%)	0.7
	4	13 (86.7%)	2 (13.3%)	
	5	7 (77.8%)	2 (22.2%)	

Int: Intravesical UNC, Ext: Extravesical UNC, *: Mann-Whitney U test, others: Fisher's Exact test

Eight patients had a contralateral renal scar on the pre-operative DMSA and no recurring contralateral reflux was observed.

Contralateral reflux was observed in 4 out of 18 children 4 years of age or younger and 2 of the 25 children older than 4 years; however, the difference was not significant. While heavy scarring was present in 5 out of 18 children aged 4 years or younger and in 6 out of 25 children older than 4 years, there was no significant difference. The contralateral reflux rate was higher in children with heavy ipsilateral scarring (6-36%) ($p=0.029$) (Table 2). Contralateral reflux was significantly higher in the heavy ipsilateral scarring group in children aged 4 years or younger (60-7.7%) ($p=0.044$) (Table 2); however, for children older than 4 years the difference was not significantly higher (16.7-5.3%) ($p=0.43$) (Table 2).

Five patients with contralateral reflux recovered within an average of 24.6 ± 12.2 months (ranging from 7 to 41 months), while one patient achieved recovery of contralateral reflux after undergoing a single session of Dx/HA implantation.

Discussion

In this study, we found the rate of the contralateral reflux developing after unilateral UNC to be 15.8%, consistent with other studies. Operative trigonal distortion, pop-off mechanism, reflux missed in VCUG, and the natural course of the disease have been emphasized in the literature for the development of contralateral reflux following unilateral UNC (2-4). In our study, we reported a distinct result from previous studies, demonstrating the development of *de novo* contralateral reflux, particularly in young children, after unilateral UNC in the presence of dysplasia as a trigonal ureteral unit.

Minevich et al. (2) and Badawy et al. (9) found that contralateral reflux rates following open and laparoscopic extravesical UNC were 5.6% and 5.9 %, respectively. In another study, Kumar and Puri (10) reported 7% contralateral reflux rate following the sub-ureteric Teflon (polytetrafluoroethylene) injection (STING). These rates found in the abovementioned studies were lower than those in other series (2,9,10). These differences may be due to the operative distortion. However, Elmore et al. (11) reported that contralateral reflux was 13% following Dx/HA implantation, while Diamond et al. (3) suggested that UNC type does not affect the risk of contralateral reflux. In addition, a series by McCool et al. (12) found only 1 to 5.6% reflux rate after unilateral Cohen UNC in patients with contralateral VUR, which resolved during the follow-up. These studies did not support the operative distortion hypothesis.

Several studies have determined the relationship between high-grade reflux and contralateral reflux to show the pop-off mechanism, but there are conflicting results about this relation in the literature (3,8,10,13). In the current study, no association was observed between VUR grade and *de novo* contralateral reflux, possibly due to the high frequency of high-grade VUR cases. The finding of a high rate of contralateral reflux in patients undergoing nonoperative follow-up in the study by Sparr et al. (14) showed that newly developing reflux may be related to the natural course of the disease or the reflux missed during voiding cystourethrography. However, in their series, Barosso et al. (15) found developing contralateral reflux in 21% of the patients during follow-up and only medium- and high-grade reflux as risk factors, which may be due to a combination of natural course and pop-off mechanism. Furthermore, developmental deterioration of the trigone may also play a role in this relationship.

Table 2. Relation of presence of heavy scar tissue in scintigraphy on ureteroneocystostomy side and contralateral reflux in different age groups

	4 years old and younger		Older than 4 years		Total	
	HS -	HS+	HS-	HS+	HS-	HS+
Contralateral reflux rate	7.7%	60%	5.3%	16.7%	6.3%	36.4%
p	0.044		0.43		0.029	

HS+: Children with heavy scarring on the ipsilateral kidney, HS-: -: Children without heavy scarring on the ipsilateral kidney, Fisher's Exact test

Ross et al. (16) showed that *de novo* contralateral reflux is more significant in children with a history of resolved contralateral reflux. McCool et al. (12) confirmed this result by showing reduced contralateral reflux while performing bilateral UNC. The relationship shown by Liu et al. (17) between contralateral scarring and *de novo* contralateral reflux can be related to the increased pressure with the disappearance of the pop-off mechanism re-appearing of reflux. These mentioned studies, contrary to our study, supported the pop-off mechanism.

While the mentioned studies focused on passive valve function, they did not consider the developmental deterioration of the trigone and the active valve mechanism. Some literature has emphasized the importance of active valve function and the histological composition of the distal ureter (6,18-21).

In the study by Lama et al. (7), it was suggested that congenital renal damage in infants with VUR, diagnosed before the first urinary tract infection, is related to urinary reflux during fetal development. Dysplasia, which is characterized by more severe scarring, was frequently observed in children, especially infants, with high-grade reflux (7,22-24). Therefore, we examined the effect of heavy scarring on the development of *de novo* contralateral reflux that may be associated with the trigone and contralateral ureteral developmental deterioration.

Izol et al. (21) demonstrated that refluxing ureters exhibit immunohistopathological abnormalities, particularly in high-grade reflux. Godley et al. (8) reported reduced resolution of reflux in infants with kidney parenchymal anomalies due to VUR, with a higher resolution rate in those with normal bladder function. This may be attributed to developmental disorders associated with bladder dysfunction and primary trigonal disease, as stated by Tanagho et al. (25). In this study, severe renal damage suggestive of congenital damage could also affect the contralateral orifice related to primary trigonal disease and developmental deterioration. Moreover, multicystic dysplastic kidney is associated with severe dysplasia, which may be due to the ureteral-trigonal developmental deterioration. The contralateral reflux rate in multicystic dysplastic kidney has been reported as 10-17%, which supports the hypothesis of this study (5,26).

The higher incidence of contralateral reflux with heavy scarring in children aged four years and younger and the recovery in all patients over time suggested the effect of developmental deterioration. Although the contralateral reflux was more frequent in patients aged four years or younger (25-8%), this difference was not statistically significant in our limited sample size. Hubert et al. (27) reported similar results in their series. In the current study, no significant differences were found between age groups in terms of heavy scarring rates; however, higher rates of contralateral reflux were found in younger patients

with heavy scarring. The occurrence of *de novo* contralateral reflux in three out of five patients aged four years or younger with heavy scarring emphasizes the clinical importance of this finding.

Study Limitations

The small sample size is a limitation of this study; however, the use of open surgery for all patients provides a standardized group. Ethical issues precluded the performance of VCUG in all patients. Since UNC has a high success rate, VCUG may not have been necessary for every patient. As this study is retrospective, histological examination of ureter tissue to elucidate the underlying mechanism could not be performed. Further studies with the histological examination could provide a definitive explanation of the mechanism.

Conclusion

This study highlights the need for further investigations into the active mechanisms and primary trigonal disease. A future study examining the relationship between renal dysplasia and histological composition of the ipsilateral and contralateral ureters may provide more definitive findings. The high incidence of contralateral reflux in children with ipsilateral heavy scarring suggests the importance of close monitoring contralateral reflux.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of The Bursa Uludağ University approved the study (approval number: 2023-2/18).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.T., H.S.D., O.K., A.C.B., F.Ç., Concept: S.T., O.K., Design: S.T., O.K., Data Collection or Processing: O.K., A.C.B., Analysis or Interpretation: O.K., Literature Search: O.K., H.S.D., A.C.B., F.Ç., Writing: O.K., H.S.D., S.T.

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