Original research article

Assessment of the Kidney structure and function in dilating vesicoureteral reflux patients with anorectal malformation: an observational study

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Abstract

Aim: the aim of this study to evaluate the kidney structure and function in dilating vesicoureteral reflux patients with anorectal malformation.

Materials and methods: This is a retrospective study based on the Author's personal experience and cases operated in the Department of Paediatrics surgery Patna Medical College and Hospital, Patna Bihar, India for 10 year. Total 150 consecutive VUR >grade III (dilating VUR or D-VUR) patients include in this study. Subjects were divided into two groups according to the presence of ARM to give ARM+ (n=20; 30 ureters) and ARM– (n=100; 120ureters). **Results:** The differences between ARM+ and ARM– for sex distribution (male: 55% vs 62%), mean incidence of all UTI (including preoperative) per patient (2.1±1.7vs 2.6±1.9), incidence of bilateral D-VUR (20% vs 38%) or mean overall duration of follow-up [defined as the period from the initial consultation to the final consultation at our institute; 6.4±1.3years andgrades of D-VUR were not significant. The incidence of BBD in ARM+ was significantly higher than that in ARM– (40% vs 10%; p=0.0007). However, differences in the mean ages of BBD patients with respect to ARM were not significantly different [7.2±2.4 years forARM+versus7.5±2.2yearsfor ARM–, p=0.62]. DMSA scans indicated that both severe multiple and diffuse renal cortical lesions (RDS: 2m, 2d) were identified significantly more often in ARM+ than in ARM– (65% versus 30%, p=0.042).

Conclusions: we concluded that the renal cortical lesions were correlated with grade of D-VUR in ARM– and RDS was significantly higher in ARM+, BBD did not appear to contribute to progressive renal dysfunction as is commonly believed.

Introduction

Vesicoureteric reflux (VUR) is the retrograde passage of urine into the upper urinary tract, during detrusor contraction at micturition. In the absence of lower urinary tract outlet obstruction and neurogenic bladder, it is considered to be primary. Primary VUR is regarded as a risk factor for urinary tract infections (UTIs) and post infectious scarring. In most patients, VUR including higher grades undergoes spontaneous resolution over a period of time. VUR has been shown to be associated with renal scarring, referred to as reflux nephropathy; 7%–17% of end-stage renal disease (ESRD) is reported to be associated with primary VUR.[1-3]There is a strong association of bladder–bowel dysfunction (BBD), VUR, and UTI.[4]Treatment strategies for VUR include surgical re-implantation of ureters or endoscopic injection of a bulking agent at the ureterovesical junction or medical treatment with low-dose antibacterial prophylaxis with the aim of preventing UTI and consequent scarring. Considerable research has been conducted on the optimal treatment for VUR, and studies have improved the understanding on renal damage associated with VUR. Milder grades of VUR are considered innocuous. Further, it is increasingly recognized that aggressive therapies for VUR may not affect renal damage or development of ESRD. As VUR is detected on investigations that are carried out after an episode of UTI, there is debate

on the need for detailed evaluation protocols for UTI. This review focuses on an evidence-based approach to the diagnosis and management of VUR. the prevalence of VUR is presumed to be 1%.[5]However, a study on normal infants and children found reflux in 28% on micturatingcystourethrography (MCU).[6] Other studies in children without predisposing conditions show VUR in 0%–30%.[7] As VUR may be subclinical, resolves with time, and requires MCU for diagnosis, determining the prevalence would require subjecting al newborns to an invasive procedure that is not possible. VUR is often diagnosed following evaluation of one or more UTI. In a large retrospective study, the prevalence of VUR was estimated at 37% in children with UTI and 34% without UTI.[8] A large meta-analysis estimated the incidence of VUR in siblings and offspring of patients with VUR at 27.4% and 35.7%, respectively.[9] Variability in the reorted prevalence of VUR is largely due to design, selection bias, and methods used for its diagnosis. Researchers believe that ~1% prevalence of VUR is conservative, with a more reliable estimate of 10%–40%.[7,10] VUR is also diagnosed in children who are evaluated for chronic kidney disease (CKD), hypertension, renal stones, and rarely for proteinuria.

Materials and methods

This is a retrospective study conducted based on the Author's personal experience and cases operated in the department of Paediatrics surgery Patna Medical College and Hospital, Patna Bihar, India for 10 years from August 2010 to July 2020.

Methodology

Total 150 consecutive VUR >grade III (dilating VUR or D-VUR) patients include in this study. Patients with neurogenic bladder due to tethered cord, spina bifida and sacral anomalies, ureteropelvicjunction obstruction, cloaca or lower urinary tract obstruction were excluded as being secondary causes of VUR, leaving 120 patients as subjects for this study. Subjects were divided into two groups according to the presence of ARM to give ARM+ (n=20; 30 ureters) and ARM– (n=100; 120ureters).

Data for gender, type of ARM, grade of D-VUR assessed by using voiding cystourethrogram (VCUG), incidence of UTI (defined as fever $>38^0$C accompanied by leukocytosis with left shift, and positive catheterized urine culture growing at least 10^5 bacteria per mL), use of prophylactic antibiotics to prevent UTI, presence of BBD (defined by the American Urological Association as a combination of at least one lower urinary tract symptom, such as presence of urinary frequency, urinary urgency, extended periods between voiding, daytime wetting, perineal or penilepainorholdingmaneuvers,withatleastonetype of dysfunctional defecation, such as constipation, or encopresis) reported by the parents or the patient in lay terms, without specific use of classification tools, duration of follow-up and a simple renal dysfunction score (RDS), based on a format approved by the Japanese Reflux Nephropathy Forum involving scoring renal cortical lesions detected on dimercaptosuccinic acid (DMSA) scintigraphy on a scale of 0–2 with 0 representing no cortical lesions, 1 representing less than two lesions or split renal function >40% and 2 representing split renal function.As part of our routine protocol for evaluating patients with ARM preoperatively for definitive corrective surgery, we performed a VCUG and contrast enema to diagnose and classify the ARM. VUR was usually diagnosed at this time, and a baseline DMSA scan was performed. By the time of preoperative assessment for ARM, almost all patients had experienced UTI as a consequence of their VUR , While prenatally diagnosed ARM was an indication for more intensive management during pregnancy, prenatally diagnosed hydronephrosis did not tend to warrant any extra attention unless it was severe, so only a few ARM− were diagnosed with hydronephrosis prenatally, and in most ARM−, VCUG and DMSA were performed only.After the first UTI, with the result that most ARM− cases did not routinely have baseline

DMSA studies. Thus, while ARM+ had DMSA scans performed before and after definitive corrective surgery, ARM− did not. Similarly, during postoperative follow-up, DMSA scans were performed at least 3 months after the last UTI in order to avoid documenting acute renal cortical lesions and at least every 2 years in all patients to update the status of renal cortical lesions.

Statistical analysis

The recorded data was compiled entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, mean and standard deviation. Test applied for the analysis were Mann-Whitney U test, the unpaired t-test, the $\chi 2$ test and the one-way analysis of variance test were used for statistical analysis. A p value less than 0.05 was considered to be statistically significant.

Results

All ARM cases were postoperative for definitive corrective surgery at the time data were collected. All ARM+ patientswerefullytoilettrainedatthetimeofBBDassessment. All urine samples were obtained by urinary catheterization.In this study the differences between ARM+ and ARM– for sex distribution (male: 55% vs 62%), mean incidence of all UTI (including preoperative)per patient (2.1±1.7vs 2.6±1.9), incidence of bilateral D-VUR (20% vs 38%) or mean overall duration of follow-up [defined as the period from the initial consultation to the final consultation at our institute; 6.4±1.3years (range: 2.0–14.8)vs6.1±0.5years(range:1.5–10.9)]andgrades of D-VUR were not significant (table 1). The incidence of BBD in ARM+ was significantly higher than that in ARM– (40% vs 10%; p=0.0007) (table 1). However, differences in the meanages of BBD patients with respect to ARM were not significantly different [7.2±2.4years (range:4.3–12.2) for ARM+versus7.5±2.2years(range: 4.2–10.1) for ARM–, p=0.62]. DMSA scans indicated that both severe multiple and diffuse renal cortical lesions (RDS: 2m, 2d) were identified significantly more often in ARM+ than in ARM– (65% versus 30%, p=0.042) (table 1). We also observed that there was no tendency for mean uptake on DMSA scintigraphy to deteriorate after definitive corrective surgery in ARM+ .

Duration of follow-up was hard to standardize because we did not have a protocol for follow-up. We calculated the mean duration of follow-up of post-ARM surgery patients with complete DMS A results, but the figure, 4.2 years(range:1.0to14.9years),was not specific enough to use meaning fully, so we abandoned using it as a criterion for comparison. To summarize, differences in sex distribution, mean incidence of all UTI per patient, mean age of patients, grades of D-VUR, incidence of BBD in ARM+ according to RDS and RDS for different types of ARM were not significant. Although the overall spectrum of grades of D-VUR was not significantly different, grade of D-VUR was significantly lower in ARM– with low RDS (p=0.0084). Inother words, there were less renal cortical lesions in more normal patients (see table 2 for RDS results according to sex, age and grade of VUR).

Table 1: Demographic and clinical characteristics for patients

Parameter	**ARM+ (n=20)**	**ARM– (n=100)**	**P value**
Male/female	11/9	62/38	0.325
Mean incidence of all UTI per patient (including preoperative)*	2.1±1.7	2.6±1.9	0.738
Use of prophylactic antibiotics, n(%)	14(70)	89 (89)	0.088
Recurrence of UTI, n(%)	1365)	63(63)	0.875
Bilateral VUR, n(%)	4 (20)	38 (38)	0.589
Severity of D-VUR, n=ureters (%)			0.136
Grade I	n=20 (66.66)	n=51 (42.5)	
Grade II	n=5(16.67)	n=53(44.17)	
Grade III	n=5 (16.67)	n=14 (11.67)	
RDS n=kidneys (%)			0.042
RDS=0 (none)	n=3 (15)	n=30 (30)	
RDS=1 (less than two lesions, split renal function >40%)	n=4 (20)	n=40 (40)	
RDS=2m (multiple lesions, split renal function <40%)	n=3 (15)	n=10 (10)	
RDS=2d (diffuse lesions, split renal function <40%)	n=10 (50)	n=20 (20)	
Presence of BBD, n(%)	8 (40)	10 (10)	0.0007
Mean follow-up period (years)*	6.4±1.3	6.1±0.5	0.948

Table 2:

	ARM+=20					ARM–=100				
	RDS=0	**RDS=1**	**RDS=2m**	**RDS=2d**	**P value**	**RDS=0**	**RDS=1**	**RDS=2m**	**RDS=2d**	**P value**
Number of kidneys	N=3	N=4	N=3	N=10		N=30	N=40	N=10	N=20	
Male:female ratio (% male)	2/1	3/1	2/1	6/4	0.782	21/9	26/14	6/4	15/5	0.411
Mean age (years)	(51.5)	(74.2)	(51)	(43.4)	0.897	(56.4)	(64.7)	(56)	(75)	0.419
Mean incidence of all UTI per patient (including preoperative)*	5.3	6.9	5.4	6.9	0.393	6.2	6.7	7.9	7.4	0.685
Severity of VUR n=ureters (%)	1.1±0.2	1.1±0.9	2.7±0.9	3.2±2.5	0.402	2.1±1.3	2.5±1.6	2.1±1.4	2.6±1.4	0.006
GradeI	2(66.67)	4 (100)	2(66.67)	5(50)		17(56.67)	17(42.5)	3(30)	3(15)	
GradeII	1(33.33)	0	0	3(30)		12(36.67)	19(47.5)	3(30)	12 (60)	
Grade III	0	0	1(33.33)	2(20)		1(3.33)	4(10)	4(40)	5(25)	
BBD (%)	0	3(75.0)	2(66.33)	4(40	0.378	2(6.67)	3(7.5)	0 (0.0)	2 (10)	0.877

Discussion

To the best of our knowledge, this is the first study to investigate correlations between D-VUR, BBD,RDS and ARM. In this study, DMSA identified diffuse renal cortical lesions in the kidneys of as many as 50% of ARM+. ARM+ also had significantly higher RDS than ARM– when differences in grades of D-VUR and incidences of UTI were not significantly different, and there were no differences in RDS related to type of ARM. In other words, RDS results were a consequence of the presence of ARM, not the type of ARM. Most strikingly, the distribution of renal cortical lesions on DMSA scans as reflected by RDS did not appear to change over time in ARM+, which was contrary to expectations. The fact that renal cortical lesions did not progress during follow-up suggested that renal cortical lesions were most likely tobe stable asscars.

Renal cortical lesions are known to be associated with D-VUR secondary to UTI because of anatomic anomalies associated with VUR,[11]or because of bladder dysfunction that has been reported in D-VUR as part of a congen- ital VUR anomaly.[12] VUR certainly increases the

risk of developing symptomatic UTI,[13]so the presence of D-VUR should be detrimental to kidney function. Capozza*et al*[14]documented that there was a different natural history for boys and girls with VUR. Sillén[15] studied VUR in infancy and found that grade V VUR was almost exclusively male and that the resolution rate for grade IV VUR was 40%–50% during the first year of life. Wennerström*et al*[16]studied the incidence of UTI sequelae and found that boys tended to have reflux-associated renal cortical lesions, while girls tended to have UTI-related cortical lesions. Although we did not observe gender differences in this study, we did observe that renal cortical lesions were correlated with grade of VUR in ARM–, with RDS=0 being predominant when D-VUR grades were lower (p=0.006). Increased awareness of the association between BBD and D-VUR led the American Urological Association to report that BBD increased the risk for breakthrough UTI in children receiving antibiotic prophylaxis, reduced the success rate for endoscopic injection therapy, increased the risk for postoperative UTI and was a risk factor for renal scarring.[13,17]In this series, as many as 40% of our fully toilet trained ARM+ patients had BBD that started initially with severe constipation requiring enemas or irrigations after anorectoplasty. In addition, constipation was reported in postoperative ARM patients, ranging from 38% to 46% purportedly related to persistent anatomic anomalies of the anorectum.[18,19] Thus, BBD and postoperative constipation might influence kidney structure and function, and we were careful to follow-up our ARM+ with BBD patients regularly for evaluation of BBD and renal/urinary tract function, and if necessary, prescribed appropriate treatment to minimize the symptoms of BBD. However, there was also no change in the distribution of cortical lesions on DMSA during follow-up based on the presence of BBD, which again suggested that renal cortical lesions were stable and not progressive. Unfortunately, our study was limited because it was retrospective and performed at a single institute. We also did not have baseline data of DSMA lesions without a history of UTI, and our sample size was too small for us to make any categorical conclusion,[20] but our data were sufficient to identify trends in various criteria (demographic data and history of UTI) that were not statistically different. By assessing the known risk factors for renal cortical lesions in D-VUR patients with respect to ARM, we hypothesize that the renal cortical lesions seen in ARM patients may be an inherent feature of the anorectal anomalies comprising ARM itself, rather than being acquired or secondary. In other words, our study demonstrates that diffuse renal cortical lesions may, in fact, be part of the clinical spectrum that manifests clinically as ARM. To validate our results, further data on the distribution of lesions need to be collected by performing DMSA routinely when ARM is newly diagnosed, followed by regular studies over time. By doing this, if lesions are present on initial DMSA studies, they can be classified as being congenital, but should no lesions be identified, then lesions must be classified as being acquired, and if they persist on repeat DMSA performed at least 3 months following an episode of acute UTI, then they should be considered to be scars. Even though there was no progression of renal cortical lesions observed during this study, follow-up should be regular, and treatment/ intervention should commence as early as possible when required.

Conclusion

We concluded that the renal cortical lesions were correlated with grade of D-VUR in ARM– and RDS was significantly higher in ARM+, BBD did not appear to contribute to progressive renal dysfunction as is commonly believed.

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