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Vesicoureteral Reflux and Reflux Nephropathy

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Abstract

Primary vesicoureteral reflux (VUR) is the commonest congenital urological abnormalities in children, which has been associated with an increased risk of urinary tract infection (UTI) and renal scarring, also called reflux nephropathy (RN). In children, RN is diagnosed mostly after UTI (acquired RN) or during follow-up for antenatally diagnosed hydronephrosis with no prior UTI (congenital RN). The acquired RN is more common in female children whereas the congenital RN is more common in male children. This observation in children might help explain the differences in the clinical presentation of RN in adults, with males presenting mostly with hypertension, proteinuria, and progressive renal failure as compared to females who present mostly with recurrent UTI and have a better outcome. Known risk factors for RN include the severity of VUR, recurrent UTI, and bladder-bowel dysfunction; younger age and delay in treatment are believed to be other risk factors. Management of VUR is controversial and includes antimicrobial prophylaxis, surgical intervention, or surveillance only. No evidence-based guidelines exist for appropriate follow-up or the management of patients with RN.

Keywords

Vesicoureteral reflux; VUR; Reflux nephropathy; Prophylaxis

Introduction

Primary vesicoureteral reflux (VUR) is the commonest congenital urinary tract abnormalities in childhood, which is diagnosed mostly after an episode of urinary tract infection (UTI). The gold standard for its diagnosis is the voiding cystourethrogram (VCUG), which is graded I to V, grade V being the most severe type. Reflux nephropathy (RN) is the renal scarring that is diagnosed in patients with VUR, mostly in association with UTI (UTI). However, renal scarring can occur with UTI in the absence of a VUR or with VUR in the absence of a UTI. Whereas the occurrence of former has been reported in the literature for a long time, the evidence for the latter is more recent and has come mostly from children with antenatally diagnosed hydronephrosis, who on post-natal evaluation are found to have VUR and renal scarring. Currently, the RN is defined as congenital (also called primary), which is a result of abnormal renal development resulting in focal renal dysplasia, or acquired, which results from pyelonephritis-induced renal injury. However, the

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differentiation of congenital versus acquired RN on the basis of preceding UTI can be arbitrary because the possibility of a pre-existing renal scar before the UTI cannot always be ruled out. The acquired RN is seen more often in females whereas the congenital RN occurs mostly in males. Some other important differences between acquired and congenital RN are shown in table 1.

The exact mechanism for renal scarring following UTI is not known, but is believed to be mediated by immunological mechanisms, macromolecular trapping and mesangial dysfunction, vascular alterations, hypertension and hemodynamic alterations¹. Renal scarring due to intrarenal reflux occurs mostly at the renal poles because the presence of extensively fused (compound) renal papillae, which are associated with reflux.² The scarring may result from a single episode of pyelonephritis, especially in young children, also called “big bang effect”³ or the process may take several years. In one study the mean time from the discovery of VUR to the appearance of renal scarring was 6.1 years⁴.

Incidence

In a cohort of pediatric patients with UTI, including 68% infants, VUR was diagnosed in 33% of cases⁵. The exact incidence of RN in children or adults is not known. The diagnosis is difficult in patients who may have already undergone the natural resolution of VUR by the time RN is diagnosed. The reported incidence of RN varies from 36% to 56% in patients with UI and VUR^{6,7}. A review of the year of publication of studies with renal scarring following UTI in children with and without VUR revealed that the rates of renal scarring in such children with first UTI have been relatively stable at 15% since 2002⁸. Congenital RN has been reported in 30% to 60% of mostly male children with VUR diagnosed as a result of antenatally diagnosed hydronephrosis, also called prenatal VUR^{9,10}.

Increasing age at the diagnosis of VUR correlates with increasing incidence of renal scarring; 10% in preterm infants, 26% in children under 8 years, 47% in children older than 8 years and 94% in adults^{11–14}. In a study involving otherwise healthy children and adolescents who were evaluated for newly diagnosed hypertension, DMSA scans revealed renal scarring in 33 (21%) of the 159 patients with a median age of 11 years; 22 patients had unilateral and 11 had bilateral scarring. The study could not define whether the RN was congenital or acquired in origin and if the hypertension was definitely the result of renal scarring¹⁵.

Risk factors for RN

It is not clear if the VUR and its severity have a causative role in the formation of renal scars or whether it is a marker for congenital mal-development such as hypoplasia/dysplasia¹⁶. Children with VUR are more likely to develop pyelonephritis (relative risk: 1.5 [95% CI: 1.1–1.9]) and renal scarring (relative risk: 2.6 [95% CI: 1.7–3.9]) as compared to those with no VUR, and children with VUR grades III or higher are more likely to develop scarring than children with lower grades of VUR (RR: 2.1 [95% CI: 1.4–3.2])⁸. The risk of renal scarring involving more than 25% of renal parenchyma is significantly higher in patients with grade III–IV (40%) VUR as compared to those with grade I–II VUR (14%) or no VUR (6%)¹⁷. Renal cortical abnormalities are more common in children with VUR even without a prior history of UTI and the abnormalities are more common in high-grade VUR. A meta-analysis of the published data revealed that renal abnormalities (per 100 renal units) occur with a mean of 6.2% in those with grades I–III VUR and 47.9% in those with grades IV and V VUR. The abnormalities ranged from 2% to 63% (mean 21.8%) of patients with VUR and 26% to 42% (mean 32.3%) of the renal units¹⁸.

VUR-related renal scarring is more common with UTI and the odds ratio of renal scarring with acute pyelonephritis in the presence of a VUR is 2.8 for patients and 3.7 for renal units as compared to those with no VUR¹⁹. The risk of renal scarring increases with constipation and voiding dysfunction. The bladder bowel dysfunction (BBD) increases risk of febrile UTI in children on antimicrobial prophylaxis for VUR to 44% as compared to 13% in those without BBD. The BBD delays VUR resolution at 24 months (31% with BBD and 61% without BBD) and the rate of postoperative UTI is greater in children with BBD (22% as compared to 5% without BBD)¹⁹.

A delay in the treatment of febrile UTI is associated with increased risk of renal injury^{20, 21}. A multivariate analysis of 158 children with febrile UTI and therapeutic delay of > 48 hours was associated with significantly increased risk of acute lesions on renal scan²². However, the Italian Renal Infection Study Trials reported that the progressive delay in antibiotic treatment of acute pyelonephritis from <1 to > 5 days after the onset of fever was not associated with any significant increase in the risk of scarring on Dimercaptosuccinic acid (DMSA) renal scans obtained 1 year later. The risk of scarring remained relatively constant at 30.7 +/- 7%. Clinical and laboratory indices of inflammation were comparable in all groups, as was the incidence of VUR²³. In another study, early and appropriate treatment of UTI, especially during the first 24 hours after the onset of symptoms, diminished the likelihood of renal involvement during the acute phase of the infection but did not prevent scar formation⁷.

Young age is believed to be another risk factor for renal scarring due to UTI and this was highlighted in the American Academy of Pediatrics recommendations on the management of UTI in infants and young children²⁴. Higher risk in infants is also acknowledged in the most recent American Urological Association (AUA) guidelines¹⁹. However, scarring does occur in adult kidneys as well. Adult pig kidneys scar as quickly as those of piglets with VUR and UTI²⁵ and scarring is known to occur in adult mature kidneys transplanted into pediatric patients²⁶. Some recent studies have reported that the age may not be a risk factor for renal scarring and the risk in older children is the same^{21, 27, 28} or even higher^{29, 30} as compared to the younger children.

Complications

The complications of RN are well-known but poorly defined because of their insidious onset and slow progression. These include hypertension, proteinuria, urine concentration defects, hyperkalemia, acidosis, and chronic kidney disease with progressive renal failure, including end-stage renal failure (ESRF) in some patients. Of these, hypertension and proteinuria are the commonest ones that have a significant bearing on long-term renal outcome and both are amenable to medical intervention.

Hypertension

The relationship between renal scarring and hypertension was first demonstrated in 1937 when the removal of a small scarred kidney cured hypertension in a 10 year old female with recurrent UTI and hypertension³¹. Hypertension occurs in 17%–30% of pediatric patients³² and 34–38% of adult patients with renal scarring^{33, 34}. Confounding factors such as increasing frequency of primary HTN in adults makes this interpretation difficult. According to a study that did survival analysis, it was estimated that 50% of patients with unilateral and bilateral renal damage would have sustained hypertension at about 30 and 22 years of age, respectively³⁵. In a follow-up lasting 15 years in pediatric patients with renal scarring, about 13 % patients at age 20–31 years became hypertensive, mostly between the ages of 15 and 30 years³⁶. The plasma rennin activity (PRA) may increase in some children with renal scars

as they grow older, but there is no direct correlation between BP and PRA, plasma creatinine concentration, or degree of scarring³⁷.

Proteinuria

Overt proteinuria, which has been reported in 21% of adult patients with RN³⁴ is a rare occurrence in pediatric patients. It results from glomerular and/or tubulointerstitial damage caused by immunologic injury, macromolecular trapping and mesangial dysfunction, hypertension, and glomerular hyperfiltration¹. Microalbuminuria, which is indicative of glomerular damage at a very early stage and precedes overt proteinuria, progressive renal damage and renal failure, has been reported in 51% pediatric patients (mean age 9.8 ± 4.2 Years) with renal scarring³⁸. Patients with RN also spill increased amount of low molecular weight proteins (LMWP) such as beta 2-microglobulin (B2M), retinol-binding protein (RBP), alpha 1-microglobulin (A1M), and N-acetyl- β -D-glucosaminase (NAG)^{39–42}.

Microalbuminuria occurs around the same time or soon after the appearance of LMWP in urine and its excretion increases with the severity of renal scarring^{39, 42, 43}.

Focal Segmental Glomerular Sclerosis (FSGS)

RN has also been associated with focal segmental glomerular sclerosis (FSGS)⁴⁴. In a histological review of 86 pediatric nephrectomy specimens from patients with VUR (with or without apparent obstruction at the vesicoureteral junction) FSGS was found in 18 (21%) patients, 9 of whom were less than 5 years old. There was no significant association between the presence (or grade) or absence of FSGS and age at nephrectomy, gender, presence or absence of obstruction, and severity of hypoplasia and/or Postnatally acquired cortical loss⁴⁵. FSGS is progressive and can occur in non-scarred parts of the kidney or in the normal contralateral kidney in patients with unilateral RN⁴⁶. The pathogenesis for FSGS in RN is not clear and has been attributed to glomerular hyperfiltration, deposition of antigen-antibody complexes, failure of mesangium to clear macromolecules, and glomerular injury due to circulating immune complexes.

Renal failure

RN is responsible for 12% to 21% of all children with chronic renal failure^{47, 48}. According to 2008 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report, RN is the fourth commonest cause for chronic kidney disease in 8.4% of the children and is seen in 5.2% of transplanted patients and 3.5% of dialysis patients⁴⁹. In the CKID study that involved a cohort of 586 children aged 1 to 16 years with an estimated GFR of 30–90 ml/min/1.73m², RN was the underlying cause for CKD in 87 (14.8%) patients. This constituted 19% of the patients with non-glomerular etiology for CKD⁵⁰.

RN in adult patients

Unlike pediatric patients in whom a diagnosis of renal scarring is prompted mostly by the occurrence of UTI, the diagnosis in adults is either a carryover diagnosis from the pediatric age group or is a result of pregnancy-related complications, recurrent UTI, hypertension, proteinuria, renal calculi or renal failure. RN in adults shows a more marked differentiation in clinical presentation between the genders. As shown in table 2, adult males with RN generally present with hypertension, proteinuria and renal failure, whereas the females present mostly with UTI and pregnancy-related complications. The males have a poorer outcome as compared to females; a difference that was previously explained on the basis of more insidious onset and hence delayed diagnosis in males and the UTI-prompted earlier diagnosis in females, and the dilution of severe cases because of earlier presentation of females due to recurrent UTI and pregnancy-related complications⁵¹. However, given the

knowledge gained in pediatric patients, it is quite possible that the adult males most probably have congenital RN as compared to acquired RN in adult females.

In a study that assessed renal function 16–26 years after the first UTI with renal scarring in childhood and compared it with an age-matched cohort, the total GFR remained unchanged, but the individual GFR of the scarred kidneys decreased significantly. The decrease in GFR was significant in those with bilateral renal scarring. The median urine albumin/creatinine ratio was 1.2 mg/mmol compared to 0.6 in those with no scarring⁵². In another study on 293 adults (mean age at presentation 31±13.4 years) with RN, females outnumbered males by a ratio of 5:1. The most common presenting complaints for both genders were UTI (65%), hypertension (20%), and proteinuria (6%). However, UTI as a presenting complaint was significantly more common in females as compared to males (72% vs. 31%) where as proteinuria was significantly more common in males (20% vs. 4%). Hypertension was also more common in males (29% vs. 18%) but the difference was not significant. VUR was present in 65% females and 75% of males. Of the 147 patients who were followed for a mean period of 6.9±3.6 years, 21 (14%) developed ESRF after a mean follow-up of 7.0±3.1 years⁵³.

The potential complications during pregnancy in adults with RN are well established. In a study on 137 such women with 345 pregnancies, the maternal complications occurred in 39% of the pregnancies, 40% patients had VUR. The complications included urine infection, hypertension, proteinuria, edema, deterioration in renal function, hematuria, and the renal stones. These complications were significantly more common in those with bilateral renal scarring or impaired renal function (plasma creatinine >0.11 mmol/l) at conception⁵⁴. In another study on 375 pregnancies in 58 women with RN, UTI was the most common complication (22.3%), followed by hypertension (4.3%), preeclampsia (10.4%), fetal loss (10.2%), and preterm delivery (24.2%). The degree of renal function at conception defined the outcome during pregnancy, with compromised fetal prognosis and the progression of maternal disease in those with serum creatinine of >0.22 mmol/L⁵⁵.

Management of VUR and RN

Antimicrobial prophylaxis

The subject of antimicrobial prophylaxis in VUR is undergoing a raging debate because of serious doubts about its usefulness as well as concerns about the risk of antimicrobial resistance, patient compliance, cost of medication, and prophylaxis-driven need for repeated renal imaging⁵⁶. In the last six years, five prospective randomized trials evaluated the role of antimicrobial prophylaxis in the prevention of recurrent UTI and renal scarring in children^{57–61}. In these studies patients were randomized to antimicrobial prophylaxis or placebo/surveillance only; one of the studies used endoscopy treatment as the third intervention⁶². Of the five studies, two included patients with UTI and VUR^{58, 61} where as the other three included patients with UTI with or without VUR. Altogether 1435 patients were randomized and included were 961 (67%). Further details on these studies are shown in table 3.

As shown in table 4, a total of 968 patients had DMSA renal scans for renal scarring. Three studies by Garin et al.⁵⁷, Montini et al.⁵⁹ and Pennesi et al.⁵⁸ reported no benefit with antimicrobial prophylaxis in children with and without VUR. The study by Craig et al reported 6 percentage points (95% CI 1–13) decrease in the number of UTIs with TMP/SMZ as compared to placebo. The results favored the use of prophylaxis in all children except those with index UTI caused by SMZ/TMP-resistant organisms⁶⁰. The Swedish Reflux Trial⁶³ demonstrated that the rate of UTI recurrence in girls was higher than boys, and that this rate can be decreased with antibiotic prophylaxis and endoscopic treatment. There was

no difference between the prophylaxis and endoscopic treatment groups⁶³. None of the five studies showed any difference in the rate of scarring with prophylaxis/endoscopy versus no prophylaxis. Meta-analysis of these studies with a total of 968 patients (including those who underwent Deflux procedure in the Swedish study) evaluated for renal scarring revealed renal scarring in 36% of cases with prophylaxis and endoscopy (Swedish trial) as compared to 33% with no intervention or placebo therapy; RR of 0.98(95% CI: 0.84–1.14; p=0.8). Very few new scars were reported during the follow-up period.

This ranged from no new scars at 2 years⁵⁸ to 4/295 (1.4%) at one year⁵⁹. Swedish Reflux Trial reported 24/201 (12%), new scars at 2-year follow-up, which included 4/68 (6%) patients in prophylaxis arm, 8/65(12%) patients in endoscopy arm and 12/68 (18%) patients in surveillance-only arm. It also showed that girls had a significantly higher rate of new renal damage on DMSA than boys. The renal damage, which was most common in the surveillance group showed a strong association with recurrent febrile UTI⁶².

The results of these studies should be interpreted with caution because the primary end-point for all these studies was UTI and as a result the data on renal scarring in some of the studies is sketchy. Furthermore, these studies had a combination of study design related limitations that related to patient inclusion and exclusion criteria, definition of renal scarring, and the duration of follow-up. This is partly reflected in the significant differences in renal scarring between the various studies. The ongoing Randomized Intervention in Children with VUR (RIVUR) study has completed randomization of 607 patients, many of whom are currently undergoing the two-year follow-up. This randomized, placebo-controlled study is evaluating the role of antimicrobial prophylaxis in the prevention of UTI (primary study end-point) and renal scarring in children less than 6 years old with grade I–IV VUR diagnosed after UTI⁶⁴

Surgical Intervention

Surgical treatment in spite of offering the quickest possible correction of the VUR has not been shown to be superior to antimicrobial prophylaxis as far as recurrence of UTI or renal scarring are concerned. This was demonstrated by the International Reflux Study^{65–67}, Birmingham Study⁶⁸, and more recently the Swedish Reflux Trial^{62, 63}. However, it has the advantage of not requiring follow-up VCUGs to the extent needed in patients on antimicrobial prophylaxis. Surgical treatment is generally recommended in patients with high grade VUR (IV and V), ineffective antimicrobial prophylaxis as demonstrated by breakthrough UTI's, patients allergic to antimicrobials, poor patient compliance, worsening of scars, and sometimes parental preference. In view of the potential pregnancy-related complications, surgical repair is also recommended in girls with VUR that persists as puberty approaches. Currently, endoscopic treatment of reflux involving subureteral or intraureteral injection of dextranomer hyaluronidase (Deflux[®]) is offered as the first-line surgical treatment in most cases. Other surgical options include laparoscopic or open surgical reimplantation, the latter being the gold standard for VUR surgery with about 98% success rate.

Surveillance only

In 2007, the National Institute for Health and Clinical Excellence (NICE) in Great Britain published its controversial recommendations on not using antibiotic prophylaxis routinely in infants and children following first-time UTI, and only selectively in recurrent UTI⁶⁹. Last year, The AUA published its guidelines on management of primary VUR in children¹⁹. The recommendations are stratified into three categories (standard, recommendation, option) based on the current available evidence, with “standard” being the most rigid statement policy. According to AUA recommendations, for children less than a year old, it is a “recommendation” to use prophylaxis for all grades of VUR diagnosed after UTI and grade

III–IV VUR diagnosed through screening, where as it is an “option” in grade I–II VUR diagnosed after screening. In children older than a year, prophylaxis is a “recommendation” if VUR is associated with recurrent febrile UTI, bladder-bowel dysfunction, or renal cortical abnormalities, in the absence of which it is an “option”. Similar recommendations have been made in children with breakthrough UTI, which includes the role for endoscopic or surgical correction of VUR ⁷⁰.

Other Management

Appropriate management of BBD is important in the prevention of recurrent UTI, help resolution of the VUR and possibly prevent further renal injury. This includes the treatment of constipation, frequent and complete voiding, biofeedback and or use of anticholinergic medication or alfa-blockers, and continuous intermittent catheterization in extreme cases. There are no evidence-based guidelines for the management of hypertension, proteinuria or other complications related to RN. Timely diagnosis and appropriate management of hypertension is essential for preserving renal function. The use of angiotensin converting enzyme inhibitor (ACEI) and/or an angiotensin receptor blocker (ARB) for proteinuria and/or hypertension is recommended. In patients with poorly functioning unilateral RN, removal of the affected kidney may be considered, keeping in mind that the nephrectomy may not cure hypertension.

Conclusion

VUR is a common urological abnormality in children and the role of antimicrobial prophylaxis or surgical intervention in the prevention of recurrent UTI or renal scarring remains controversial. The true extent of RN and its clinical course in different age groups, including adults, is not known. No evidence-based guidelines exist for the management of RN in any age group. Timely diagnosis and appropriate management of hypertension, proteinuria, and/or progressive renal disease is necessary to preserve the renal function. Appropriately designed prospective studies are needed to further define the clinical and biological characteristics of RN.

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Table 1**Congenital Versus Acquired Reflux Nephropathy (RN) in Children**

	Acquired RN	Congenital RN
Time of Occurrence	Postnatal	Prenatal
UTI before diagnosis	Common	Uncommon
Age distribution	All pediatric age groups	Mostly in younger children
Gender distribution	Predominantly females	Predominantly males
Grade of VUR	Mostly low-grade	Mostly high-grade
Dysplastic features on renal histopathology	No	Yes

UTI: Urinary tract infection; VUR: Vesicoureteral reflux

Table 2

Reflux Nephropathy in Adults

	Males	Females
UTI	Uncommon	Frequent
Plasma creatinine	Higher	Normal
End-stage renal failure	More common	Less common
VUR	High grade/bilateral	Low grade/unilateral
Proteinuria	Frequent/severe	Infrequent/Less severe
Hypertension	More common	Less common

UTI: Urinary tract infection; VUR: Vesicoureteral reflux

Table 3

Recent randomized Studies on Antimicrobial Prophylaxis and Renal Scarring

Authors Year of Study	Randomized/Placebo-Controlled	Patient Age	Total Number of Patients Studied	Males/Females	Patients Included	Number of Patients with VUR	VUR Grade	Duration of Follow-Up (Months)
Garin et al, 2005	Yes/No	3 month –18 years	218	40/178	UTI ± VUR	113	I-III	12
Pennesi et al, 2008	Yes/No	0 month–2 ½ Years	100	48/52	UTI + VUR	100	II-IV	24 – 48
Montini et al, 2009	Yes/No	2 months–7 years	338	104/234	UTI ± VUR	128	I-III	12
Craig et al, 2009	Yes/Yes	0–18 years	576	207/369	UTI ± VUR	243	I-V	12
Swedish Reflux Trial, 2010*	Yes/No	1–2 years	203	75/128	UTI + VUR + AD	203	III –IV	24

VUR: Vesicoureteral reflux; UTI: Urinary tract infection; AD: antenatal dilatation (4% of the patients)

Table 4Renal Scarring in Recent Randomized Studies in Patients with UTI $\pm$ VUR

Authors & Year of Study	Number of Patients with DMSA Renal Scan	Renal Scarring on DMSA		Relative Risk % (95% CI)
		Prophylaxis/Endoscopy *	No Prophylaxis	
Garin et al, 2005	218	7/100 (7%)	6/118 (5%)	1.37 (0.47 to 3.96)
Pennesi et al, 2008	100	22/50 (44%)	18/50 (36%)	1.22 (0.75 to 1.98)
Montini et al, 2009	295	50/187 (26.8%)	33/108 (30.5%)	0.87 (0.60 to 1.26)
Craig et al, 2009	154	35/71 (49%)	38/83 (46%)	1.07 (0.77 to 1.50)
* Swedish Reflux Trial, 2010	201	82/133 (62%) *	45/68 (66%)	0.93 (0.75 to 1.15)
COMBINED	968	196/541 (36%)	140/427 (33%)	0.98 (0.84 to 1.14)

VUR: Vesicoureteral reflux; UTI: Urinary tract infection

* includes 40/68 patients on prophylaxis and 42/65 patients who underwent endoscopy