

A Changing Scenario in Our Understanding of Vesicoureteral Reflux in Children

In this issue of the Journal is an article on the long-term clinical outcome of primary vesicoureteral reflux (VUR) in children in Sri Lanka(1). It is a subject that has been extensively researched and discussed by the pediatricians, pediatric nephrologists and pediatric urologists. This is because VUR is the commonest urological abnormality in children, it is associated with an increased risk of urinary tract infection (UTI), and VUR and UTI are believed to cause permanent renal parenchymal damage in young children. The natural course of VUR is spontaneous resolution in most of the cases, particularly in those with low-grade VUR. The International Reflux Study in Children reported that VUR disappeared in more than 80% of undilated and about 40% of dilated ureters(2). Schwab and colleagues reported that grades I-III VUR resolve at a rate of 13% per year for the first 5 years of follow-up and 3.5% per year during subsequent years; whereas grades IV and V VUR resolve at a rate of 5% per year(3). In the International Reflux Study in Children, resolution of VUR was significantly better in grade III versus grade IV VUR(4). A systematic review of published literature on the resolution of VUR revealed that increasing age at presentation and bilateral VUR decrease the probability of resolution, and bilateral grade IV VUR has a particularly low chance of spontaneous resolution(5).

The management of VUR involves treatment and prevention of UTI with antibiotic

prophylaxis until the resolution of VUR. Surgical reimplantation or endoscopic treatment is generally performed in those who fail conservative management. This approach is primarily driven by the belief that acute pyelonephritis in children is a major cause of morbidity because of its association with renal scarring, which carries a risk of subsequent hypertension, toxemia of pregnancy, and significant renal damage, including end-stage renal disease. According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) annual report for 2004, 471 (8.3%) of the 5651 children with chronic renal insufficiency (CRI) had reflux nephropathy, which, according to the registry, is the third commonest cause of CRI after obstructive uropathy and renal aplasia or dysplasia(6). A comprehensive literature review on febrile UTI in children by the Committee on Quality Improvement (Subcommittee on Urinary Tract Infection) of the American Academy of Pediatrics identified children less than two years old as being at highest risk of renal damage with febrile UTI(7).

However, in spite of a seemingly straightforward diagnosis and treatment, serious doubts have arisen over the last few years on the current management of VUR in children. This, to a large extent, is a result of systematic review of published literature and observations made on patients with VUR with no UTI, such as those with VUR diagnosed during followup for antenatal hydronephrosis (prenatal VUR) and sibling screening. Some of the major controversial issues are as follows.

How reliable is the diagnosis of VUR?
Voiding cystourethrogram (VCUG) is the gold

standard for diagnosing and grading VUR. Yet the results of the procedure can be affected by size and position of the catheter, rate of bladder filling, height of the column of contrast media, state of hydration of the patient, and volume, temperature, and concentration of the contrast medium(8). The result of a VCUG is also affected by the number of bladder fillings during the procedure; three cycles give more positive results than two cycles(9). The intermittent nature of VUR was the basis for International Reflux Study in Children using two successive negative VCUGs for the confirmation of VUR resolution. Another controversial issue with the VCUG has been its timing in relation to the febrile UTI. This is because of a risk of overestimating VUR if the VCUG is done during the acute phase of a UTI(10).

How strong is the association between VUR, UTI, and renal scarring? In the International Reflux Study of children with grade III and IV VUR, the frequency of acute pyelonephritis was not significantly different in children with and without resolution of VUR. UTI occurred in 36% children with persistent VUR, 38% of those with diminished VUR, and 33% of those in whom VUR ceased(11). In another study that involved 222 patients, no relationship was seen between severity of VUR, UTI symptoms, and renal scarring(12). Renal scars in febrile UTI are known to occur in patients without VUR.(13,14) Another reason for increasing scrutiny of the relevance of VUR in renal injury is the detection of renal lesions by nuclear scans in many children with prenatal VUR with no history of UTI(15). Such observations raise the possibility of pre-existing renal parenchymal pathology that is associated with VUR and is not a result of UTI, and puts into question the published literature from the days when antenatal ultra-sonography and DMSA scintigraphy were not available.

Does long-term antibiotic prophylaxis make a difference? Serious doubts exist on the relevance of long-term antibiotic prophylaxis for VUR. Guidelines from the American Academy of Pediatrics(7), American Urological Association(5), and Swedish Medical Research Council(16) recommend using long-term antibiotic prophylaxis, and yet at the same time acknowledge lack of evidence for this recommendation. Shindo and colleagues observed that renal scarring, the injury presumably having been initiated by VUR, can progress despite correction of the reflux and prevention of UTI(17). Arant and colleagues reported that, despite good medical management, even mild and moderate VUR can be associated with renal injury(18). In a study of 51 children with VUR (grades I-IV), the prophylactic antibiotic was discontinued after a mean period of 4.8 years. After a mean followup period of 3.7 years, only 11.8% of patients had a UTI and no new scars developed in any of the patients. The argument in support of long-term prophylaxis is further weakened by doubts about compliance with prolonged medication. One study found that trimethoprim was not detectable in the urine in 31% of the subjects whose parents reported giving them the medication for long-term prophylaxis.

Is surgical intervention better than prophylaxis? Contradictory reports have been published on the ability of antireflux surgery in preventing acute pyelonephritis and renal scarring. Recurrent UTI is as common after surgical correction as it is in those treated medically, and surgical correction of VUR in most cases does not prevent or reduce the progression of renal scarring(19,20). The International Reflux Study reported that the outcome for renal function, including GFR, is not improved by surgical correction of VUR in children with bilateral VUR(21).

A meta-analysis on the predictability of renal parenchymal damage by diagnosing VUR in hospitalized children with febrile UTI showed that a positive VCUG increases the risk of renal damage in hospitalized UTI patients by about 20%, whereas a negative VCUG increases the chance of no renal involvement by just 8%. The authors concluded that VUR is a weak predictor of renal damage in children hospitalized with UTI(22). A recent Cochrane Review of the effectiveness of long-term antibiotics for preventing UTI concluded that most published studies to date have been poorly designed, with biases known to overestimate the true treatment effect(23). In yet another systematic analysis, the authors questioned the value of identification of VUR after a symptomatic UTI, and the effects of various interventions on the occurrence of UTI and subsequent renal parenchymal damage. The study concluded that it is uncertain whether the identification and treatment of children with VUR confers clinically important benefit and intervention, including antibiotic prophylaxis or surgery for VUR, is better than no treatment(24).

Conclusion

The association between VUR and renal scarring has been demonstrated in some but not all studies. Also, the rationale for long-term antibiotic prophylaxis in VUR has not been studied by a well-designed, prospective, controlled trial. The conflicting data becomes even more confusing with frequent clinical observations of no VUR in many children with recurrent UTI and/or renal scarring, or the absence of UTI and/or renal scarring in many children with VUR. The role of voiding dysfunction in UTI and/or VUR is not very clear. The clinical and possibly genetic differences between VUR diagnosed during sibling screening, VUR diagnosed during follow-up for antenatal

hydronephrosis, or VUR diagnosed after UTI are not fully understood and need further research.

As of now, the prudent thing is to treat UTI effectively and use long-term antibiotic prophylaxis in young children until the resolution of VUR. Appropriate management of constipation and/or voiding dysfunction may help decrease the incidence of breakthrough UTI and facilitate resolution of VUR. Endoscopic correction of VUR with dextranomer/hyaluronic acid copolymer (Deflux) should be considered in those with high grade VUR or recurrent UTI inspite of antibiotic prophylaxis. Besides those with a history of UTI, a VCUG should be considered in children with bladder dysfunction, children with prenatal hydronephrosis/hydroureter, and those with unilateral multicystic dysplastic kidney. Screening for VUR should be offered to first-degree relatives of children with VUR and off-springs of parents with VUR.

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