



Pediatric vesicoureteral reflux: Slow but steady steps



Vesicoureteral reflux (VUR) is a common urological anomaly that is found in 1% of children. VUR can cause recurrent febrile urinary tract infection (UTI). The recurrent infections can result in renal scarring, which can lead to renal hypertension and end-stage renal disease. Thus, our therapeutic goal is to prevent febrile UTI in the short term and, in the long term, to preserve renal function by inhibiting renal scarring and the associated complications.

The exact pathophysiology of VUR and VUR-related complications is not yet known. We do not know why VUR shows great differences in severity depending on the patient. Genetic studies are being conducted on this aspect. VUR is a disease that is included in congenital anomalies of the kidney and urinary tract (CAKUT). In the article “Genetics of vesicoureteral reflux and congenital anomalies of the kidney and urinary tract”, Lee et al. [1] summarized VUR and CAKUT. CAKUT is a genetically heterogeneous group of disorders that are caused by mutations in genes involved in the kidney development process. Among the genes and signaling pathways, those involved in the progression of CAKUT have been evaluated. More than 20 genes and pathways have been identified that act at each step of kidney development. Although it is still too early to apply these genetic findings in clinical practice, advances in sequencing and bioinformatics technologies illustrate the future possibility of early diagnosis, better management, and genetic counseling.

Over the past 20 years, changes have taken place concerning how much to evaluate for VUR when febrile UTI occurs. Abdelhalim and Khoury [2] organized about this in their article, and explained the advantages and disadvantages of the top-down approach, which is the most used in Korea. Historically, children with any degree of VUR were thought to be at risk of renal damage and

underwent surgical correction. On the basis of this concept, the American Academy of Pediatrics suggested a bottom-up approach in 1999 [3]. However, subsequent studies have reported that VUR does not always have serious consequences and that treatment is not always required because spontaneous resolution is common. This has shifted the evaluation policy for VUR to a top-down approach that relies on a dimercapto-succinic acid (DMSA) renal scan and limits the number of voiding cystourethrograms (VCUGs). The management has changed because there is no need to find VUR without renal damage. Moreover, it is argued that there is no clinically meaningful difference in the management of VUR after an acute-stage DMSA scan. There are reports that VUR detected by a defect seen on the DMSA renal scan is not related to long-term renal scarring. This points out a problem of the top-down approach, in addition to the limitations of the DMSA renal scan (economic burden, radiation, sedation, and interobserver variability), which forms the basis of the top-down approach. As a result, the American Academy of Pediatrics in 2011 recommended that ultrasonography, although less sensitive than the DMSA renal scan, be used to detect anatomical abnormalities that require further evaluation [4]. However, there is as yet no established guideline for VUR diagnosis.

New imaging studies and biomarkers have been investigated for the diagnosis of clinically meaningful VUR. We have been using ultrasonography, DMSA renal scans, and VCUG for decades to diagnose VUR. However, the pain and UTI risk of VCUG, poor sensitivity and low positive predictive value of ultrasonography, and the aforementioned limitations of the DMSA renal scan have yet to be overcome. According to Prasad and Cheng [5], there is a movement to provide anatomical and functional data in one study by using magnetic resonance urography, and interactive

magnetic resonance voiding cystography has also been attempted. Another recent trend is to diagnose VUR without using contrast media or catheterization, as in the case of intravoxel incoherent motion diffusion-weighted imaging in magnetic resonance imaging [6]. Studies of biomarkers are constantly being reported, but it is difficult to find reliable markers.

There is as yet no established guideline for the management of VUR diagnosis. Many studies are retrospective, heterogeneous, and lack qualified randomized controlled studies. Large-scale, prospective, multicenter studies are needed to determine whether short-term management of febrile UTI can be prevented with various managements and whether long-term reductions in renal function can be prevented. Studies to date have provided evidence for the recurrence of febrile UTI. A typical example is continuous antibiotic prophylaxis (CAP). CAP has been around for over 40 years, but much controversy remains about its effectiveness. Lee and Park [7] revisited the current evidence of CAP in their article. Recently, the RIVUR (randomized intervention for children with vesicoureteral reflux) trial demonstrated that CAP decreased the risk of recurrent UTI in patients with grades I–IV reflux [8]. However, evidence is still lacking as to whether renal scarring and the reduction in renal function can be prevented. Because CAP cannot block renal scarring, there is still a claim that it is unnecessary.

However, these treatments cannot be seen to be meaningless owing to the lack of evidence in terms of prevention of renal scarring or renal insufficiency. To assess renal scarring and associated renal function, studies should be conducted on larger groups of patients for longer periods of time than has been done in studies of febrile UTI. It is also important to recognize the limitations of the guidelines and to recognize that individual cases of VUR may vary.

In the surgical treatment of VUR, endoscopic injection therapy (EIT) has grown considerably in the past decade. According to Kim et al. [9], despite the excellent short-term success rate, increasing reports of complications such as delayed ureteral obstruction and concerns about durability limit the use of EIT. Nevertheless, EIT is a convenient method with a single procedure. Further randomized, prospective study is required to determine the optimal use of EIT in the management of VUR. Laparoscopic surgery has been on the rise since the mid-2000s, and robotic surgery has been expanding in the 2010s. Although laparoscopic surgery is not widely used at present, good results have been reported in experienced centers. Robotic surgeries have been used more often, but the therapeutic results of these

surgeries require further validation.

Secondary VUR differs from primary VUR in clinical presentation and therapeutic effect. Typical cases of secondary VUR are posterior urethral valve (PUV) and neurogenic bladder. The severe form of PUV is actively treated. However, there are various degrees of severity in PUV as described by Nakai et al. [10]. The relatively minor urethral deformity associated with VUR has not received much attention owing to difficulty in understanding its clinical manifestations. Urologists need to be constantly interested in this, and efforts are needed to diagnose and classify these deformities. The presence of VUR in patients with neurogenic bladder has a low likelihood of spontaneous resolution, and the success rate of treatment is low. It is important to increase the capacity of the bladder, to increase compliance, and to treat the involuntary detrusor contraction of the bladder. Individual bladder dynamic evaluation is required, and customized treatment should be provided accordingly. In the review done by Wu and Franco [11], they emphasized that the surgeon who approaches a patient with a neurogenic bladder should always have the phrase "Caveat Emptor" in mind since the management of VUR in the neurogenic bladder is not as simple as in the normal bladder and is fraught with difficulties and complications.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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