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Review Article

New Attention to Vesicoureteral Reflux In Children: A Review Article

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ABSTRACT

Background and Aim: Vesicoureteral reflux (VUR) as a known cause of urinary tract infection (UTI), renal scarring, and nephropathy, is congenital and often familial. The prevalence of VUR is unclear, although most cases of VUR resolves spontaneously, the management of children with VUR is controversial. The purpose of this review was to evaluate VUR in order to provide an update on management to improve its prognosis.

Methods: The articles from several sources, including PubMed, Scopus, Embase, Google Scholar, Web of Science, and the Directory of Open Access Journals, were included.

Conclusion: Due to various complications, VUR is very scary for patients or families, and special attention is needed. A challenge for pediatric nephrologists is the early diagnosis of VUR and the progressive complications of kidney disease. There is no internationally accepted, uniform, evidence-based algorithm for the assessment of reflux anywhere.

Keywords: Chronic kidney disease, Vesicoureteral reflux, Antenatal hydronephrosis, Urinary tract infection

Introduction

Retrograde flow of urine from the bladder into the ureter and renal pelvis secondary to a dysfunctional urethral junction is called vesicoureteral reflux (VUR) [1-3]. Reflux into the parenchyma of renal is defined as intrarenal reflux [4, 5]. VUR is either primary or secondary, although primary VUR is the most common congenital malformation of the urinary tract, which is inherited in an autosomal dominant manner [1, 2, 4]. Due to the significant rate of transmission of VUR from parents to their children, estimates have shown that up to 66% of children of parents with VUR are affected. Also, 75% of children identified with VUR by sibling screening are asymptomatic [4, 5]. Secondary VUR may occur after surgery, such as a kidney transplant, correction of a urethral junction obstruction, and decompression of the ureter, or due to increased bladder pressure [3-5]. Bacteria van transfer from the bladder to the ureter, which is facilitated in these patients, predisposing the patient to urinary tract infection (UTI) [4, 5]. Without appropriate treatment, 30-60% of patients with UTI and VUR develop renal scar and reflux nephropathy (RN) [2-5].

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The complications of nephropathy caused by VUR are high blood pressure due to renin, proteinuria, kidney failure, impaired physical growth, and complications during pregnancy. Complications of RN include renin-induced hypertension, proteinuria, kidney failure, impaired physical growth, and morbidity during pregnancy [4-6]. Abnormal development of the kidney in RN leads to focal or extensive renal dysplasia [4, 5]. Due to more aggressive management, there are probably fewer children with severe reflux complications.

Incidence and prevalence

Inheritance of primary VUR is autosomal dominant with variable penetrance [4-6], while this is likely underestimated due to phenotypic heterogeneity and lack of diagnostic measures, such as voiding cystourethrogram (VCUG) [4]. The prevalence of VUR varies from 1-2% in healthy asymptomatic children to 8-50% in children with UTI [2-7]. After performing VCUG, most children with UTI diagnosed with VUR are females [2, 3] but VUR often diagnosed during the evaluation of antenatal hydronephrosis is seen more in males [4]. Due to the high rate of UTI in uncircumcised boys and girls older than one year, VUR is more likely to be diagnosed [5, 6]. In an article, the prevalence of VUR in those with normal kidneys who had VCUG for other reasons, such as the diagnosis of hydronephrosis was 17.2% and in children with UTI, it was 31.1% [6].

Anatomy

To prevent VUR, the ureter-bladder junction between the bladder mucosa and the detrusor muscle is usually oblique [2-5]. The muscle fibers of the ureter extend to the trigone of the bladder and merge with the fibers of the opposite ureter [3-4]. Due to the integration of the fibers, both ureters are easily fixed inside the trigone of the bladder. There is no true valve at the junction of the ureter and the bladder, but as the bladder fills, the intermural ureter is compressed under the mucosa of the muscular wall of the bladder, preventing VUR. The anatomical location and tone of the orifice ureter in the trigone also prevent reflux [4]. If the submucosal ureter between the mucosa and the detrusor muscle is very short or absent, or in the case of the lateral or proximal dystopia of the orifice ureter in the bladder, VUR occurs [2-5].

Natural history of VUR

There is potential kidney damage in patients with VUR that may have no real clinical consequences in the diagnosis of VUR itself except for the long-term use of antibiotics, parental and patient anxiety, invasive imaging, and the possibility of surgical intervention [5, 6]. The clinical importance of VUR is based on the fact that it can predispose the patient to UTI, renal damage, hypertension, proteinuria, and end-stage renal disease (ESRD) [8-13]. The adverse effects of sterile VUR on the kidneys are still debated [9-11, 14]. Evidence of renal scarring is present in 40% of children with symptomatic VUR [11]. The harmful effect of VUR on the kidneys is associated with frequent UTI, bladder dysfunction, and detrusor pressure [11]. Primary VUR generally improves with age, especially in patients with VUR and without risk factors, and this is accompanied by the lengthening of the submucosal part of the ureter with the overall growth of the body [2, 3, 6]. Other factors associated with VUR recovery include older age at diagnosis, ureteral dilatation and tortuosity, low-grade VUR, and the absence of bowel-bladder dysfunction [3-7].

Clinical presentation of primary VUR

VUR usually causes no symptoms [2, 4, 5]; primary VUR is often diagnosed during the follow-up of congenital kidney and urinary tract disease, during family screening of a patient with VUR, and after a UTI [4, 5]. About 6% of patients with ESRD have VUR as an etiology [13]. VUR is associated with an increased risk of complications in pregnant women, such as preeclampsia and UTI [3-5]. Renal scarring is the cause of this problem, and prevention of renal scarring should be a key goal of VUR management [2-5].

VUR and UTI

VUR does not cause UTI, but by increasing the possibility of transmission of microbes, it reduces the time of progression from lower UTI to pyelonephritis [4, 5]. This can be related to a variety of mechanisms but is exacerbated by bacterial endotoxin in ureteral tonicity, leading to transient low-grade VUR that reduces bacterial clearance from the urine [4, 5, 13]. Other risk factors for UTI in patients with VUR are severe hydronephrosis, dilatation, or stasis of urine in the urinary collection system. Pyelonephritis can lead to scarring in the kidneys as a result of the inflammatory reaction, which is called reflux nephropathy [2]. Post-infectious scarring is most likely to occur in the first year of life, and the pattern of VUR in males differs from that observed in female infants [1, 4, 5, 12]. Bilateral renal abnormalities, recurrent febrile UTI, and decreased GFR were identified as very important risk factors for scarring [5, 10]. Circumcision is an important risk factor for UTI in boys [4, 7].

Diagnosis

Ultrasonography is the initial modality for the evaluation of urological abnormalities, hydronephrosis, and UTI in children. Ultrasound is generally poor in detecting VUR and is normal in low grades of VUR, but has the advantage of avoiding radiation complications [5, 6]. Contrast VCUG or radionuclide cystogram is an important diagnostic tool for VUR [1, 15-17]. VCUG evaluation is considered necessary in patients with recurrent febrile UTI and in the first febrile UTI in children younger than two years if there are abnormalities on renal and bladder ultrasound [2, 6, 7, 15]. There are two types of VUR that occur during bladder filling, called hypotensive VUR, and VUR during discharge is called high-pressure VUR. Spontaneously resolving hypotensive VUR is significantly less likely [2-5].

Radiation exposure to a radionuclide cystogram is significantly less than to a contrast-enhanced VCUG but provides more anatomic information [2, 4]. For further evaluation, a radionuclide cystogram is preferred because of less radiation, although it is difficult to determine changes in the severity of VUR [2-3]. Contrast-enhanced ultrasound is used in the evaluation of VUR due to the advantage of no exposure to ionizing radiation and relatively comparable diagnostic accuracy to VCUG [18]. However, where diagnostic accuracy is excellent, this method is highly operator-dependent [18].

VUR assessment

Despite recent advances in science and technology, the evaluation and treatment of VUR are still controversial, and there is still great heterogeneity in evaluation and treatment methods [15].

Some authors have recommended VCUG for children with atypical features (non-*E. coli,* significant family history) or recurrent UTIs [2].

Most authors have recommended VCUG in children younger than 2 years following a first febrile UTI with major renal and urinary tract abnormalities, poor urine flow, or when a non-*E coli* infection is diagnosed [4]. All cases of recurrent febrile UTI need VCUG. VCUG is not indicated in older children with febrile UTI or recurrent cystitis [2].

Management of patients with VUR includes observation, low-dose antibiotic prophylaxis, endoscopic injection, and ureteral replantation surgery [4, 6].

The main purpose of the evaluation is to determine how and when to carry out the treatment [6]. The extent of VUR was often the sole determinant of treatment decisions, but today other important factors are also important. Treatment decisions should be based on the degree of VUR, age, sex, the occurrence of UTI, and the presence of renal scarring on a dimercaptosuccinic acid (DMSA) scan [6, 15, 16].

Treatment approaches

The main goal of VUR management and treatment is to reduce the chance of infection and scarring [7, 8]. Treatment is non-surgical (observation and antibiotic prophylaxis), or surgical methods [7, 16].

Observation

The best and least complicated method is “observation” because it avoids medical intervention [2-7]. However, for adequate and accurate monitoring of the patient’s condition, regular and periodic visits and follow-up of clinic and paraclinic tests are necessary. In addition, the medical team and parents should always ensure that any UTIs are identified and managed. UTI treatment should be started as soon as possible, but if there is recurrent UTI, a different management strategy should be chosen [7]. It should be noted that this method is only suitable for patients who have a relatively low risk of kidney scarring [5-7].

Antibiotic prophylaxis

In all methods, the first-line treatment is antibiotic prophylaxis, which is very effective in preventing UTIs [2-4, 7]. Antibiotic prophylaxis for at least one year is recommended for most patients and should be considered first-line treatment for children aged 1-5 years with VUR grades III-V) [4, 7]. However, long-term antibiotic prophylaxis has not been approved as a treatment option for all patients of all ages, conditions, and genders [7, 8, 19]. The optimal duration of antibiotic prophylaxis in asymptomatic patients has not been determined [6-8, 19].

VUR does not cause an infection, but it may shorten the time it takes for cystitis to progress to an upper UTI [6, 8]. This is an option to perform a VCUG control intermittently [6]. If progressive infections occur under this antibiotic prophylaxis, another treatment should be performed. In children who receive prophylactic antibiotics, the possibility of antibiotic resistance is high. Children with VUR and bladder and bowel dysfunction (BBD) highly benefit from this method [6].

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Surgery

To reduce the recurrence of febrile acute urinary infection, scarring, and other complications of VUR, surgical procedures can be performed with cystoscopic suburetral injection and ureteral reimplantation [2, 4, 6].

Endoscopic injection

In recent decades, a new treatment called cystoscopic suburethral injection with different materials has become common [2, 4, 6]. Endoscopic injection is recommended only in special cases, not in all cases. The long-term efficacy of endoscopic injection has been proven in various studies and is approved for persistent cases as a second-line treatment or as a first-line intervention in severe VUR (especially in older children) [6-8, 20-22].

Ureteral reimplantation

Reimplantation of the ureter is recommended for patients who do not respond to suburethral injection and also as the first-line treatment in high-risk groups (children older than one year with VUR grade V and children over five years with high-grade bilateral VUR) [6, 7]. This method is associated with a high success rate (more than 90%) in grade Z≤ IV VUR [7]. This invasive method requires hospitalization and a long recovery time [2, 4]. Up to 9% of children who undergo open surgery have complications [7]. Laparoscopic and robotic procedures are more popular than ever because they reduce the complications of invasive surgery [7, 20]. Complications are one of the most controversial aspects of endoscopic and open surgical treatment. In endoscopic treatment, a material that is biocompatible, non-absorbable, and without local inflammatory reaction should be used. Secondary obstruction is an important complication in endoscopic treatment and open surgery [2, 4].

Conclusion

The purpose of this study was to pay more attention to qualitative studies in the field of VUR in children, focusing on the need for more and more extensive research in this field. According to the current findings, it is recommended to carry out more studies on early diagnosis and careful long-term management of this disorder. Currently, more emphasis is placed on an individualized and risk-based approach, with less use of antibiotics as long-term prophylaxis due to high complications and drug resistance, reducing the use of VCUG and surgical procedures. Long-term follow-up of patients after endoscopic treatment or ureteral reimplantation with VCUG evaluations seems unnecessary, due to high treatment success [5-7].

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declared no conflict of interest.

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