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VESICOURETERAL REFLUX, ETIOLOGY, DIAGNOSTICS, TREATMENT AND COMPLICATIONS- REVIEW ARTICLE

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Abstract

Primary vesicoureteral reflux (VUR) is the commonest congenital urological abnormality in children, which is associated with an increased risk of urinary tract infection (UTI) and renal scarring, also called reflux nephropathy (RN), with a risk of late consequences: proteinuria, focal segmental glomerular sclerosis, hypertension, and chronic renal disease (CKD).

Key words:vesicoureteral reflux, abnormality, children.

Introduction

Vesicourethral reflux (VUR), unilateral or bilateral, is the most common congenital urological abnormality in children and is associated with an increased risk of urinary tract infections and renal scarring. It is also called reflux nephropathy.

In the European Guide [1] VUR in children is defined as retrograde flow of urine from the bladder to the ureters and to the kidneys, and is an anatomical and/or functional disorder with potentially serious consequences such as kidney scar formation, arterial hypertension, and renal failure. VUR can appear in primary and secondary form [2, 3].

Primary VUR is caused by congenital abnormality of the urethral orifice and ureterovesical junction (UVJ), but there is a normal functioning of the lower urinary tract. Primary VUR occurs in 30% to 50% of children with urinary tract infection (UTI), and in about 10% of patients who are prenatally diagnosed with second- or third-degree of hydronephrosis [4].

Secondary VUR, on the other hand, is an acquired condition that occurs with/or as a result of obstruction or dysfunction of the lower urinary tract such as: obstruction of the bladder neck, dysfunction of the posterior urethral valve, and neurogenic bladder dysfunction. In both cases, the UVJ does not function normally as a one-way valve, allowing bacteria from the lower urinary tract to flow to the upper urinary tract, which is, as a rule, a sterile environment [2, 3].

Etiology, pathophysiology and epidemiology of primary VUR

As a rule, urine flow is one-way from the kidneys to the bladder, which is provided by the normal UVJ, which prevents retrograde flow of the urine to the kidneys, and functions as a flap, or valve mechanism. In fact, it is not an anatomical structure of the valve, but a mechanism that relies on the length of the ureter, in the so called "tunnel", its oblique insertion, and the support of the detrusor muscle behind the ureter. A rise in intravesical pressure causes compression of the ureter with no retrograde flow of urine to the kidneys.

However, disruption of the development of UVJ leads to an abnormal shortening of this tunnel, which is the basis for the development of primary VUR. Normally the ratio of the length of the intramural tunnel to the length of the urethra should be 5: 1, which is not the case with VUR when the ratio is usually 1.4: 1, which means that when the tunnel is shorter, the probability of VUR occurrence is higher. The diagnosis of VUR is usually established when there are symptoms of UTI, so that the exact prevalence cannot be determined with certainty, but it is considered that in children who do not have accompanying disorders it is about 0.4-1.8%, and is much higher in children with UTI (15-70%) [2,5].

It is considered that there is a familial predisposition to VUR [5,7], and in families where VUR exists, the prevalence reaches up to 30%, and in those whose parents had VUR in childhood it can range up to 66% [8]. In terms of gender, VUR is more common in younger male children, and occurs at a higher age in female children. Also, in males, the degree of VUR is higher, but at the same time there is a greater chance of its spontaneous resolution, which is not the case in females [1, 2, 8].

Clinical expression

VUR is manifested either as asymptomatic hydronephrosis diagnosed prenatally by ultrasound or as UTI manifested by recurrent febrile episodes [2, 3].

However, urinary tract infection in children up to one year of age is relatively difficult to recognize due to the presence of nonspecific symptoms and signs: insufficient progress with or without fever, vomiting, diarrhea, or lethargy. Older children may have frequent urges to urinate or frequent urination, difficulty urinating, incontinence, dysuria with fever, or abdominal discomfort or pain.

Although the presence of fever indicates a possible infection, it is still insufficient to establish the diagnosis. Children with reflux nephropathy may complain of headaches due to present arterial hypertension, and may even show symptoms of heart failure or uremic symptoms of renal failure. On palpation, palpable sensitivity of the abdomen and renal lobes may be present.

Diagnostic work-up

According to the Recommendations of the European Association of Urology [1], the diagnostic work-up should aim at evaluating the health and development of the child, presence of UTI, renal status, presence of VUR, and lower urinary tract function. A detailed medical history, physical examination, including measurement of pressure, analysis of urine with proteinuria, urine culture, if indicated, and measurement of serum creatinine are taken first. The standard methods of diagnosis and decision for therapeutic treatment are: visualization methods that include ultrasound and renal bladder ultrasonography (US), voiding cystourethrography (VCUG) and radionuclide examinations - direct radionuclide cystography (DRC) and renal scan with 99m Tc-dimercaptoxucinic acid (DMSA scan). The standard criterion for the diagnosis of VUR is detection on VCUG, especially at the initial work-up. VCUG provides precise anatomic detail and allows grading of VUR (Figure 2) [9, 10].

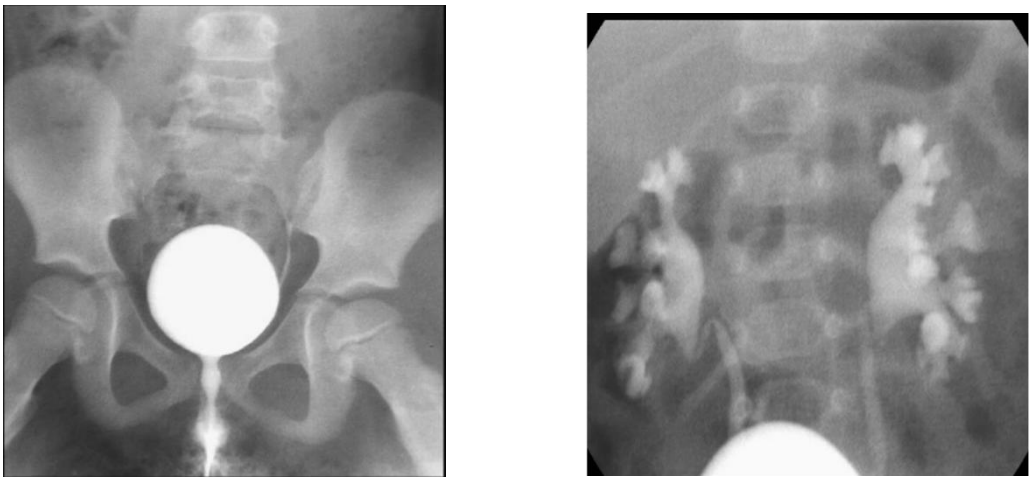

Figure 2. Radiographic grading of VUR: grade 1 (left) and grade 3 (right)

The recommendations [1] advise clinicians to use the established VUR grading system introduced by the International Reflux Study Committee (Table 1) in order to avoid interbuster variations [9].

Although this method is the gold standard for the diagnosis of VUR, it remains quite aggressive. Also, having in mind the fact that this method identifies a population with a clinically insignificant VUR, it may never show a clinical problem that can create a condition for unnecessary treatment [1, 5, 10, 11]. It must not be forgotten that VUR does not necessarily cause damage to the renal parenchyma after febrile UTI [12, 13]. At the same time, one-third of newborns and about 37% of children aged 1-5 years may have renal injury in the absence of VUR [12, 13].

VUR can spontaneously resolve and not every VUR and febrile UTI can lead to scarring. According to this, the VCUG method cannot fully define which population will be at risk of complications.

Table 1- Grading system for VUR on VCUG, according to the International Reflux Study Committee (10)

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system;
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

VUR = vesicoureteral reflux; VCUG = voiding cystourethrography

In recent years, a new method of assessing VUR and urethra in children has been developed - voiding ultrasonography with second-generation ultrasound contrast [14].

Using the Technetium-99m dimercaptosuccinic acid or 99mTc, DMSA scan in renal scintigraphy provides visualization opportunities of cortical tissue, its identification and monitoring of renal scarring, which is a key point in the treatment of VUR [1, 11-16]. The best timing for realization of the scan is 6 months after UTI, since only then can the loss of renal function, the thinning of the cortex, and the formation of scars be really diagnosed. The presence of an abnormal DMSA scan in children with febrile UTI is strongly correlated with VUR (15-16). Non-invasive kidney and bladder US is a standard procedure in children with a prenatal diagnosis of hydronephrosis [1].

According to the results of several studies [12], "normal" US does not exclude the existence of a significant degree of VUR, as well as a "positive" finding, which does not predispose a disorder, indicating the need of usage of both methods (US + VCUG).

However, it should be noted that there is still no consensus on which diagnostic methods should be used in children with febrile UTIs. Thus, there aretwo approaches: "bottom-up" and "top-down" (Figure 5) [12]. The "bottom-up" approach, which is most commonly used in children aged 0-2 years, involves performing a VCUG with the US, and if VUR is positive, further evaluation involves performing a DMSA scan [1, 12].

The "top-down" approach involves first performing a DMSA scan after febrile UTI to determine the presence of cortical defects or areas of reduced radio receiver download, and then performing VCUG to confirm the existence of VUR. Performing a DMSA scan > 6 to 12 months after febrile UTI can determine the presence of a permanent renal injury [12]. This approach allows patients with an orderly scan to avoid further invasive examination [1].

Therapy

There are mainly two approaches of treatment: conservative and surgical [1].

Conservative: This type of treatment is based on the proven evidence that VUR may resolve spontaneously in younger people. Conservative therapy is based on the understanding that VUR can resolve spontaneously, mostly in young patients with low-grade reflux, hence treatment is aimed at

preventing the onset or recurrence of febrile UTI. It includes careful monitoring (at 6-12 months) with visualization methods (US, MCUG-radioisotope MCUG or DMSA renal scan, nuclear cystography or DMSA scanning), intermittent antibiotic or continuous antibiotic prophylaxis [1,17,18]. While the benefits of continuous antibiotic prophylaxis at low grades of VUR cannot be confirmed, the results of many studies have shown that this treatment effectively prevents further kidney damage, especially in patients with third- or higher-grade VUR [1, 2, 5]. However, there is still no precise answer to the question to whom and for how long this treatment should be applied.

Surgical: The following methods are used: endoscopic techniques with injection of correction agents for II-IV degree VUR and ureteral reimplantation. The success rate of endoscopic intervention is usually high (60-90%) and largely depends on the grade of the VUR [1, 2, 5, 6, 19]. There are 2 types of techniques: STING (subureteral transurethral injection) and HIT (hydrodistension implantation technique).

The STING technique uses application of a subretinal teflon injection, but this material is no longer used due to its side effects, and instead another approved agent (dextranomer hyaluronic acid copolymer) is applied. The modification of this technique is called HIT and there is evidence of its greater success [5].

Open neoureterocystostomy or ureteral reimplantation is the "gold standard" for surgical correction of the VUR, with a success rate of 95% regardless of the grade of the VUR, which corrects an inadequate ureteral length of the urethral canal [1, 5, 19].

According to the EAU Guidelines on Vesicoureteral Reflux in Children [1], all patients with VUR should be given continuous antibiotic therapy regardless of the grade of VUR, the presence of renal scarring, or symptoms in the first year of life. Surgical correction should be considered in the presence of a high degree of VUR (grade IV / V), but there is still no consensus when it should be performed and which type of intervention should be used, although for a lower grade of VUR endoscopic techniques are preferred.

However, the choice of treatment depends on: the presence of renal scarring, cortical abnormalities, the clinical course, the grade of VUR, the involvement of both kidneys, and bladder function.

Complications

Reflux nephropathy (RN) and renal scarring. A VUR that does not spontaneously recede can lead to adverse effects on the kidney and renal function. Therefore, the term reflux nephropathy (RN) [20, 21] was introduced by Ransley and Ridson in 1979.

They also determined the pathophysiology of RN, which involved the association of VUR with UTI, chronic pyelonephritis, and renal scarring [22]. The association between VUR and UTI with potentially serious consequences, which will eventually lead to RN and renal failure, is very well documented with results from a series of clinical and experimental studies [20–24].

Also, the grade of VUR and the occurrence of renal scarring has been confirmed in a number of published studies, and the predictive risk factors for their occurrence have been identified [20, 23, 25-31]. Meta-analyses of Shaikh *et al*. [28], as well as of Faust *et al*. [29], have shown an increased risk of renal scarring in children with VUR compared to those without VUR. Almost all published results found a strong and significant link between the grade of VUR and the presence of renal scars. In the literature, other risk factors for scar development include: male sex, diagnosis of VUR at an older age when treatment is delayed, and higher number of UTI [27, 32].

From a pathophysiological point of view, scarring is thought to occur in the so-called paradoxical defensive response to the bacterium, but also as a result of cell death caused by the toxicity of the bacterium itself (usually *Escherichia coli*) [32].

Even in the absence of urinary tract infection, VUR accompanied by an increased bladder pressure is able to lead to the formation of renal parenchymal scars to which the kidneys are more susceptible in young children. During urination, an increased bladder pressure is transmitted to the kidney cups and renal tubules, which can lead to rupture of the tubules by extraction of the urine into the surrounding parenchyma, which eventually leads to immune-mediated interstitial nephritis and further to renal injury - scar. Reduction in functional renal mass caused by the interaction of pathogenic factors causes compensatory hemodynamic changes in renal flow and glomerulonephritis.

Over time, these compensatory changes become inadequate resulting in unwanted features that can cause hyperfiltration and glomerulosclerosis, which can progress to renal failure.

Hypertension

It develops in adolescents as a complication of VUR in childhood, more precisely in RN [23, 25], in about 10% of cases. In the study of Lahdes-Vasama *et al*. [33] hypertension was diagnosed in 11% of patients with the finding that diastolic blood pressure was significantly higher in those with renal scarring than in those without scarring. The results of several studies show that hypertension occurs in patients who are diagnosed with VUR in the childhood, have extensive areas of renal scarring as well as scarring of both kidneys [23, 34].

In most adults with hypertension, childhood dysfunction has been shown to result in renal dysfunction and / or elevated blood pressure [23, 29].

Proteinuria and focal segmental glomerular sclerosis - Overt proteinuria is rare in pediatric patients with RN, while in adults it has been reported in 21% of cases [35].

It results from glomerular and/or tubulointerstitial damage caused by immunologic injury, macromolecular trapping and mesangial dysfunction, hypertension, and glomerular hyperfiltration. Microalbuminuria, as a precursor to glomerular and progressive renal impairment and renal failure, has been reported in 51% of pediatric patients with renal scarring [36]. RN is also associated with focal segmental globular sclerosis (FSGS).

In histopathological analysis of nephrectomized childhood patients with VUR, FSGS was found in 21% of patients. FSGS is a progressive process and can occur in parts of the kidney without scarring, but also in a normal contralateral kidney in patients with unilateral RNA [37]. The pathogenesis of FSGS in RN is unclear and is attributed to glomerular hyperfiltration, deposition of antigen-antibody complexes, and glomerular damage due to circulating immune complexes.

Renal dysfunction and renal failure - Primary VUR, actually the created scars, are associated with renal dysfunction. The results of most studies that were focused on the risk factors for developing renal dysfunction and/or chronic kidney disease in children diagnosed with VUR in the childhood (27, 33, 38-41) identified the following: proteinuria, increased creatinine concentration in plasma, scarring of both kidneys, male sex, arterial hypertension, and low GFR. Silva *et al.* [40] found that when VUR is diagnosed (> 24 months), fifth degree VUR, scarring of both kidneys, and slowing of VUR diagnosis by > 12 months after UTIs were independent predictors of chronic kidney disease (CKD).

According to a report from the NAPRTCS study (North American Pediatric Renal Trials and Collaborative Studies), RN is the most common cause of CKD in children, in about 8.4%, while in 5.2% of transplant patients and in 3.5% of dialysis patients [41]. In our recent study, independent predictors of CKD were microalbuminuria, years since the first episode of VUR, and scarring of both kidneys [42].

Conclusion

Vesicourethral reflux is the most common congenital urological abnormality in children and is associated with an increased risk of urinary tract and kidney scar infections, or reflux nephropathy. However, despite great efforts, the recommendations of professional associations and institutions did not come out with a consensus on optimal management of VUR, in terms of diagnostic procedures, treatment options and the most effective treatment timing. However, prompt diagnosis and appropriate management of hypertension, proteinuria, and/or progressive renal disease is necessary to maintain renal function. Therefore, properly designed studies are needed to further define the clinical and biological characteristics of reflux nephropathy.

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