Vesico-Ureteric Reflux in Children

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The retrograde flow of urine from the bladder to the upper urinary tract is an abnormal situation in the human being, known as vesico-ureteric reflux (VUR). It results either from an intrinsic anatomical deficiency of the vesico-ureteral junction, or from increased bladder pressure, due to mechanical or dysfunctional vesicourethral obstruction.

The recognition of the association between VUR, urinary tract infection (UTI) and renal scars, has led to an increased study of this disease in the last two decades.

Incidence

The incidence of VUR in childhood is not exactly defined, due to the paucity of prospective studies in normal children, as well as to the fact that reflux improves with age [35,37,69]. It is known that 0.5-1 % of asymptomatic children have VUR, but the incidence rises to 29-50 % in patients with UTI [37]. It occurs more frequently in siblings of children with VUR, as well as in children whose parents presented VUR (up to 66 %). The incidence in black girls is only 10 % of that seen in caucasians. These data suggest a genetic inheritance with a dominant autosomic pattern [7,37,46,47].

Approximately 80 % of newborn babies with VUR are males. After the first months, however, the incidence in girls rises and surpasses that of males by a 4:1 proportion [11,21,37]. These differences suggest other multifactorial components in the genesis of VUR, since although considered congenital in newborns, it is acquired in older children, probably due to vesical dysfunction [46,47].

Physiopathology

The efficacy of the vesico-ureteral junction depends on passive and active components. The oblique extension of the intramural ureter, the relationship between its caliber and length, and the correct location of the ureteral orifice in the trigone are included among the passive components [16,29,64]. The distal fixation of the longitudinal muscular fibers of the terminal ureter to the trigone and proximal urethra, and their contraction during voiding, actively preclude lateralization of the ureteral orifices, thus avoiding VUR [29,64]. There is a direct relationship between the morphological deterioration of the ureteral orifices, their lateralization and the intensity of VUR [37,39].

Vesical dysfunction is documented in 18-25 % of children with VUR, in the form of non-inhibited bladder contractions or vesicosphincteric dyssynergy that increase intravesical pressure and decompensate the uretero-vesical junction [24,34,66].

The association of VUR with UTI represents a threat to the renal tissue, due to the risk of pyelonephritis that eventually evolves to scarring of the renal tissue. These lesions may be focal or diffuse, occurring more frequently in the renal poles, where the collecting ducts drain to complex concave papillae that enable more easily pyelotubular reflux of infected urine, resulting in what is known as intrarenal reflux [51,52]. Some authors argue that high-pressure intrarenal reflux of sterile urine may also damage the kidneys [27,52,54].

The acute inflammatory changes of reflux pyelonephritis may be reversed if prompt antibiotic treatment is initiated [31,50]. It is unknown which pyelonephritic areas will develop scars, but once the process is initiated, it progresses despite cure of VUR and UTI [56]. Between 30 and 70 % of children with VUR have scars, characterized by parenchymal retraction and replacement by fibrosis, associated with dilatation and distortion of underlying calices [37,61,62]. Macroscopically, the kidneys contract in size and become irregular in their surface, with seg-

mental areas of tissue retraction and cortical scarring. In the scarred areas, pathological examination shows glomerular and arteriolar sclerosis with focal tubular atrophy associated with irregular interstitial fibrosis [13].

The risk of developing scars is greater when pyelonephritis occurs during the first year of life [72]. In general, the scar takes 21 months after the onset of pyelonephritis to assume its definite form [10]. In some instances scars may remain occult longer, until the neighbouring tissues undergo hypertrophy [10]. Around 50 % of children with high grade VUR have renal scars when first seen [59]. Sometimes children with low-grade VUR may present extensive scarring, that suggest previously higher grades of VUR with spontaneous improvement [69].

Deterioration of renal function occurs due to parenchymal loss, and also to vascular and circulatory changes that possibly cause hyperfiltration of the residual glomeruli [72]. Functional impairment has a slow progression, occurring in 25 to 30 % of the case [12]. Contralateral kidneys without VUR may sometimes present pathological abnormalities, a hormonal factor being suspected [3].

Reflux nephropathy, as these abnormalities are known, produces hypertension and proteinuria secondary to focal glomerular sclerosis, and in late stages, renal insufficiency [10,12,13,32]. Another consequence is the growth arrest of the affected kidney, even in the absence of significant scarring [42,53]. Body growth may also be impaired, resuming its normal rate after cure of VUR [18,44].

The clinical importance of reflux nephropathy can be portrayed by the fact that it is the main etiological factor in 34 % of hypertensive children, as well as in 30 % of children and adolescents with terminal renal insufficiency [9,65].

Symptomatology

VUR has no symptoms; the clinical picture is related to UTI and pyelonephritis, the age of the patient and the virulence of bacteria. Infants and small children may present nonspecific symptoms, such as fever, lethargy, anorexia, nausea, vomiting and growth arrest. Older children may have voiding symptoms, occasionally associated with abdominal or lumbar pain and fever [68,70]. In some patients, VUR is suspected by asymptomatic bacteriuria, hematuria or proteinuria. In rare instances, asymptomatic VUR is a late discovery in children with hypertension or renal insufficiency [68].

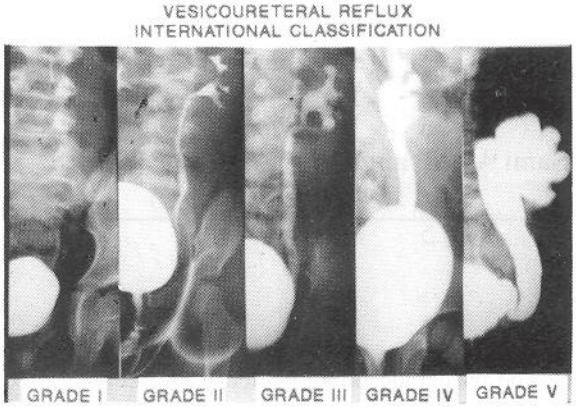

Figure 1. IRSC (International Reflux Study in Children) grading of VUR based on degree of dilatation of the pelvicaliceal system and the caliceal fornices, the papillary impressions on the calices, and the dilatation and tortuosity of the ureter (36).

Suspicion of VUR may also be raised during intrauterine life, since it is responsible for 10 % of cases of fetal hydronephrosis [21]. In these cases, it is possible to observe intermittent hydronephrosis, when the fetal bladder is full.

Diagnosis

Diagnosis of VUR is necessarily confirmed by a voiding cystourethrography (VCU), which documents its grade and discloses other anatomical abnormalities of the bladder and urethra. In order to avoid chemical cystitis, dilute contrast must be used, in a volume proportional to body weight. It is recommended to wait at least two weeks after the last episode of UTI, until it is performed under adequate sterile conditions [36,68]. An international classification of VUR has been established, according to its intensity (Fig. 1) [36]. Radioisotopic cystogram can also be employed, with the advantage that its radiation dose is 50-100 times lower. Although it has greater diagnostic accuracy, due to the prolonged exposition time, it does not characterize anatomical details as precisely as the radiographic cystography. It is a useful method for repeat follow-up studies [20,36,71].

Ultrasonography alone has no value in diagnosis of VUR, but is a valuable tool in showing upper tract dilatation, as well as cortical irregulaties that

suggest scarring [14,21]. Cystoscopy is presently not considered an important diagnostic method, being reserved for preoperative evaluation of the contralateral ureteral orifice in some cases of unilateral VUR [68].

Renal scintigraphy (RS) with Tc99 DMSA (dimercaptosuccinic acid) is employed to evalute the extension of the early pyelonephritic proccess, and of the late scarring areas [20,25,56]. This investigation has a high sensitivity and specificity, in agreement with pathological findings in 97 % of the cases [40,55]. The finding of decreased cortical uptake during UTI suggests pyelonephritis and indicates the need of a VCUG in order to document VUR [55]. RS must be repeated 4-12 weeks after cure of infection, to assess the persistence of hypoactive areas; when present, as in 42 % of the cases, they suggest that scarring is already present in these areas [40,56,72].

At the time of diagnosis, 50 % of children with high grade reflux (G III-G IV) present renal scars [59,61,62]. However, a normal DMSA scan does not exclude renal lesion, since there are medullary hypoactive areas that are not viewed by this method [20].

Radioisotopic renogram with I^{131} Hippuran, Tc99m DTPA (diethylene-triamino-pentaacetic acid), or Tc99m MAG-3 (mercaptoacetyltriglycine) enables quantitative functional assessment of the kidneys, but does not contribute to the diagnosis of VUR. Between 25 to 30 % of children with VUR develop functional abnormalities [12].

Whenever the child presents voiding abnormalities, such as urgency, frequency or enuresis, bladder instability should be suspected and an urodynamic evaluation warranted. Although such symptoms may be prominent in the history of many refluxive children, significant urodynamic abnormalities may sometimes be discovered in otherwise asymptomatic patients with VUR [2,45]. Uninhibited bladder contractions and vesicosphinteric dyssynergy are the most common findings [24,34,66].

Bacteriological studies can identify different strains of fimbriated E coli. However, other non-fimbrated bacteria may also be responsible for development of renal scars in cases of VUR [56].

Treatment

The main therapeutic goal in VUR is the prevention of renal damage caused by pyelonephritis. This can be achieved either by medical treatment, with prolonged antibacterial prophylaxis that protects the urinary tract from being infected, or by surgical means, with correction of reflux itself.

In order to avoid UTI, continuous low-dose chemoprophylaxis is recommended, particularly in patients with low grade VUR [67]. The most widely used drugs are trimethoprim, alone or in its association with sulfamethoxazole, and nitrofurantoin. Particularly the latter has good acceptance due to its high urinary concentration and low intestinal levels [8].

Equally important are hygienic and dietary measures that help maintain the stability of the perineal, preputial or introital flora [37,72]. In uncircumcised boys the need of antibacterial prophylaxis is greater due to increased risk of ascending UTI [31]. Since high pressure voiding favors persistence of VUR, it is important to identify and treat bladder dysfunction [2].

Theoretically, low dose chemoprophylaxis should be maintained continuously while VUR persists; cure is documented by 2 negative VCUG, separated by 1 year interval [37]. In children older than 5 years of age, prophylaxis is recommended only if there is symptomatic UTI, since asymptomatic bacteriuria in this age group needs no treatment [8,43].

It is known that the intramural ureteral segment grows with age, and a spontaneous cure of VUR can be expected in most cases, low grade reflux having a greater percentage of resolution. This normalization occurs more often under 5 years of age, being rare after puberty [1,19,48,54]. Between 20 and 30 % of children have spontaneous cure in a period of 2 years, raising to 50 % in 5 years [4,23].

Recent studies have shown 82 % of cure in G I VUR, 80 % in G II, and 46 % in G III, after 5 years. Results were better in left unilateral reflux (74 %), followed by bilateral (60 %) and right unilateral VUR (46 %) [4,6]. No difference between boys and girls was observed [63,70].

Pyelonephritis with new renal scars during prophylaxis was observed in only 10 % of children with G I VUR, and in 28 % of those with G II [4]. However, only a very low percentage of these groups develop hypertension, proteinuria or renal insufficiency [8]. Therefore, there is no formal indication for surgery in these patients, except in those who cannot adhere to medical treatment [43,67].

The percentage of spontaneous cure in VUR G IV is much lower, around 12 %, being worse in bilateral cases. Of these, 20 % are cured in the first 2 years, and only 40 % after 5 years [22]. Some children reach puberty with persistent reflux. Due to these facts, it is logical to suppose that surgery is indicated in patients with high grade reflux, particularly those who did not benefit from chemoprophylaxis, prepubertal girls who are in greater risk of UTI due to future sexual activity, or patients with vesicourethral dysfunction [67].

Although recent studies in patients with high grade reflux have shown no significant advantage of surgery over medical therapy after 5 years, regarding renal function, scarring and growth, there is no study that follows the same group of patients longer; since the medically treated patients are prone to more episodes of UTI with pyelonephritis, it is likely that they will present more scars in the long run [60,67]. Furthermore, there still remain unanswered questions of how long should prophylaxis be maintained in a child with anxious or uncooperative parents, as well as which are the criteria of cure in patients with recurrent UTI episodes.

Indication for surgery depends therefore, on several factors besides grade of VUR, including age and compliance to medical treatment. There is a formal indication in children with high grade reflux below 1 year of age, particularly in the presence of other anatomical abnormalities that preclude spontaneous cure of reflux, such as ureteral duplication and paraureteral diverticula [17,37,60].

Surgery has an average success rate of 95 %, with complications in less than 5 % [24,38,60]. Preoperative urodynamic evaluation is important to exclude vesico-sphincteric dysfunction that compromises surgical results; recurrence of reflux and ureteral obstruction are seen in up to 30 % in this group of patients [2,34,58].

All surgical techniques have the same goal: to create or elongate the submucosal ureteral tunnel; when the ureter is dilated or redundant, it must be shortened and tapered before reimplantation, maintaining its blood supply [68]. Our personal preference for surgical treatment of primary VUR has been the extra-vesical Gregoir-Lich procedure, in which the ureterotrigonal insertion is preserved, and the terminal ureter buried in a long submucosal tunnel [5]. It was employed in more than 1500 patients in the last 3 decades, including simultaneous bilateral operation. Overall cure rate is 98 %, with ureteral obstruction seen in only 1.5 %, due mostly to initial cases in which the terminal ureter was extensively dissected, causing periureteral fibrosis. VUR persisted in only 0.5 %, and all cases were successfully reoperated with the same technique, employing a longer tunnel [6].

More recently, endoscopic injection of substances such as teflon, collagen, and polyvinyl alcohol foam, or autologous fat and muscle, has been employed for reinforcement of the submucosal segment of the ureter. Although not universally accepted, due to the known but low risks of particle migration (teflon), immune response (collagen) and recurrence (autologous fat, collagen), this technique has high rates of success, with the advantage of being an outpatient procedure that can be repeated when necessary [15,22,33,43,57].

Our unpublished personal experience with teflon injection in 45 patients with VUR (grades II-IV) has been satisfactory, with cure rates of 87 % after the first injection and 100% after reinjection, even in cases of complete pyeloureteral duplication (4 patients).

The results of the International Reflux Study in Children show that UTI occurs in both medically and surgically treated children (39 % of the cases), but it is clinically more severe in the first group [30,60]. New scars were seen with equal frequency in both groups after 5 years (12-22 % in the first group and 13-25 % in the second) [17,49,60]. However, while in the medically treated group 60 % of the patients still have VUR after 5 years, only 1 % of those operated still present it, indicating that they have a lesser chance of UTI in the late follow-up [2,41,49].

It is important that all children under medical or surgical treatment be followed even after cessation of reflux, in order to assess late hypertension or renal insufficiency [60].

Conclusion

Medical treatment of VUR represents an advance compared to the previous almost uniform indications of surgical treatment. The final goal of both medical and surgical treatment must be the cure of reflux itself, as well as prevention of new renal scars.

In patients with low gade VUR (G I and II), med-

ical treatment is efficient in preventing UTI and renal scars, allowing spontaneous cure of reflux to occur in most cases, consequent to maturation of the vesico-ureteral junction.

Due to intrarenal reflux of infected urine, pyelonephritis with renal scar formation occurs in the majority of patients with high grade VUR (G III and IV). There are still controversies regarding the best treatment for this group of patients. Although early medical treatment and surgery are equally effective in reducing UTI episodes and new scar formation, long term chemoprophylaxis is associated with a low percentage of spontaneous cure of high grade VUR after 5 years, when compared to surgical treatment. Therefore, medical treatment implies a much longer surveillance period, with proportionally more episodes of UTI.

The choice between the two methods in high grade reflux should be individualized, according to clinical and social conditions. Particularly in very young children or in prepubertal girls, we recommend primary surgical correction.

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