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VESICOURETERAL REFLUX: WHY WE CAN'T AGREE ON ITS MANAGEMENT ! AN EVIDENCE BASED APPROACH

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Summary.- *Vesicoureteral reflux remains one of the most controversial subjects in paediatric urology. The flooding of publications on reflux makes the understanding of this anomaly and its treatments quite opaque. Evidence Based Medicine might be a helpful tool to clarify the various approaches of reflux reflected in 6.715 publications found on Medline with the key-words "vesicoureteral reflux" and "vesicoureteric reflux". These articles were critically reviewed and graded according to EBM scorings, with regard to their methodological designs. It appears clearly after this review of literature concerning VUR that most of our beliefs are based on low evidence publications and that EBM has not sufficient arguments to establish recommendations for diagnostic and treatment of VUR. It appears yet that antenatal dilatation of the urinary tract and symptomatic UTIs justify looking for VUR. Surgery should be discussed in recurrent UTIs or deterioration of renal function. There is no consensus in the case of persistent asymptomatic VUR, indication and duration of antibioprophylaxis, and choice of radical treatment.*

Keywords: *Vesicoureteral reflux. Evidence-based medicine. Urinary tract infection. Renal anomalies. Treatment.*

Resumen.- *El reflujo vesicoureteral sigue siendo uno de los temas más controvertidos en urología pediátrica. El aluvión de publicaciones sobre reflujo hace que el entendimiento de esta anomalía y sus tratamientos sea bastante opaco. La medicina basada en la evidencia puede ser un instrumento útil para clarificar los diferentes abordajes del reflujo reflejados en 6.715 publicaciones encontradas en Medline con las palabras clave "vesicoureteral reflux" y "vesicoureteric reflux". Estos artículos han sido revisados críticamente y clasificados de acuerdo con puntuaciones de medicina basada la evidencia, en relación con sus diseños metodológicos. Después de esta revisión de la literatura sobre el reflujo vesicoureteral, parece claro que la mayoría de nuestras creencias están basadas en publicaciones de baja evidencia y que la medicina basada la evidencia no tiene suficientes argumentos para establecer recomendaciones para el diagnóstico y el tratamiento del reflujo vesicoureteral. Parece sin embargo, que la dilatación prenatal del tracto urinario y las infecciones sintomáticas justifican investigar la existencia reflujo vesicoureteral. La cirugía debería discutirse en casos de infecciones urinarias recurrentes o deterioro de la función renal. En el caso del reflujo vesicoureteral asintomático persistente no existe un consenso sobre indicación y duración de la profilaxis antibiótica y la elección de un tratamiento radical.*

Palabras clave: *Reflujo vesicoureteral. Medicina basada en la evidencia. Infección urinaria. Anomalías renales. Tratamiento.*

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INTRODUCTION

Vesicoureteral reflux (VUR) remains a controversial and confusing subject as shown by the avalanche of data (6715 hits) found on a Medline search. VUR is defined as the intrusion of bladder urine into the upper urinary tract because of a defective ureterovesical junction. The confusion is exacerbated by the fact that two different entities are hidden under this same name: the "reflux disease" due to a malformative ureterovesical junction, and the "reflux symptom" which is the consequence of a lower tract dysfunction. These two entities represent two different populations, two different therapeutic approaches and two different outcomes (Table I) although there is a grey zone between the two groups.

Is VUR dangerous?

The pathophysiology of VUR and the possible links between VUR, urinary tract infections (UTI) and parenchymal anomalies remain unclear.

VUR can cause acquired anomalies in the renal substance ("reflux nephropathy"), or can be associated with congenital structural anomalies of the renal tissue ("reflux dysplasia"). The insult caused by VUR itself can either be due to the intrusion of infected urine into the renal substance (bacterial insult), and this is the most commonly accepted danger related to VUR, or can be due to the abnormal urine pressure exerted by reflux on the papillae (urodynamic insult), or to abnormal biochemical or immunological reactions caused by the presence of bladder urine in the renal parenchyma (biochemical insult) (Figure 1).

Not one but four factors may play a role in the pathophysiology of VUR: the virulence of bacteriae and their reservoirs, incompetent vesico-ureteric junction, renal parenchyma and bladder and bowels dysfunctions.

UTI

VUR and UTI are often associated but there is no evidence of causal relationship (1). Eighty eight per cent of cystographies performed in children with VUR have sterile urine at the time of diagnosis which does not confirm that UTI causes VUR (2) (III/B), and 60% of febrile UTI have no demonstrable VUR. Mild VUR does not increase the incidence of UTI, pyelonephritis, or renal scarring after acute pyelonephritis (I/A) (3). Moreover, there is a high prevalence of VUR detected in infants by prenatal diagnosis before the occurrence of any UTI (4) (III/B). Thus, VUR and UTI seem to be independent pathological factors that may potentiate each other (1). The central question is how does the urinary tract get infected? For many, the main infection pathway is the ascent from the lower to the upper urinary tract although rarely demonstrated. Other pathways have been suggested such as haematogenous or lymphatic, but none have been validated yet.

Renal anomalies

Thirty to 60% of refluxing units are associated with renal anomaly at the time of diagnosis (5) (III/B). Renal anomalies can be congenital as seen in prenatally diagnosed

TABLE I.

	VUR symptom	VUR disease
Presentation	UTI	Prenatal diagnosis
Sex	Girl	Boy
Age	Child	Newborn/Infant
Ultrasound	Normal	Dilatation
Cystography	Grades I-II-III	Grades IV-V
DMSA	Normal	Abnormal
Resolution	High	++ (<50%)
Etiology	Bladder dysfunction	Renal dysplasia Abormal UVJ
Treatment	Bladder training	Surgery

VUR before any UTI. Male children seem more likely to have congenital type of renal anomalies (4) (III/B). Experimental studies suggest that abnormal insertion of the ureteral bud could induce abnormal differentiation of metanephros ("renal dysplasia") (6). After a first UTI, an abnormal DMSA scintigraphy is found in 9.5%, with no demonstrable VUR in most cases (7) (IIb/B). New renal damage appeared after FUTI, independently from the existence of VUR (8) (III/B).

VUR is a weak predictor of renal damage after FUTI (9) (IIb/B). Moreover, renal anomalies may progress in VUR even with long-term careful management as reported by the International Reflux Study group (IRS) (10) (IIb/B).

All the difficulty with renal lesions is that there is no established way to distinguish congenital structural lesions ("dysplasia") from acquired anomalies ("reflux nephropathy") and no way to establish whether a scar is new or is the natural progression of an abnormal islet of dysplastic parenchyma. Hence, the terms "scars" or "reflux nephropathy" are confusing and should then be avoided.

Hypertension

Five to 27% of children with renal damage will develop hypertension (11) on a long term basis. Whether renal damage is the consequence of pyelonephritis and/or reflux dysplasia remains unclear (12-13) (III/B).

End-stage renal disease (ERSD)

Twenty five per cent of end-stage renal disease (ESRD) can be attributed to VUR related parenchymal anomalies in the Italian pediatric population (14) (III/B). This rate is evaluated at 5 to 10% in the Australian adult population (15) (III/B). Modern approach of VUR is not accompanied by a reduction of the incidence of VUR-related ESRD (16) (III/B).

Relationship with bladder dysfunction

In infants

Higher voiding pressures and a dyssynergic patterns of micturition are associated with primary VUR in infants, when compared to normal lower urinary tract (17) (IIa/B). This association predominates in males, may be relevant in the pathogenesis of VUR and influences its resolution pattern.

Different voiding patterns are reported in infants with dilating VUR when compared with healthy infants (18) (IIa/B).

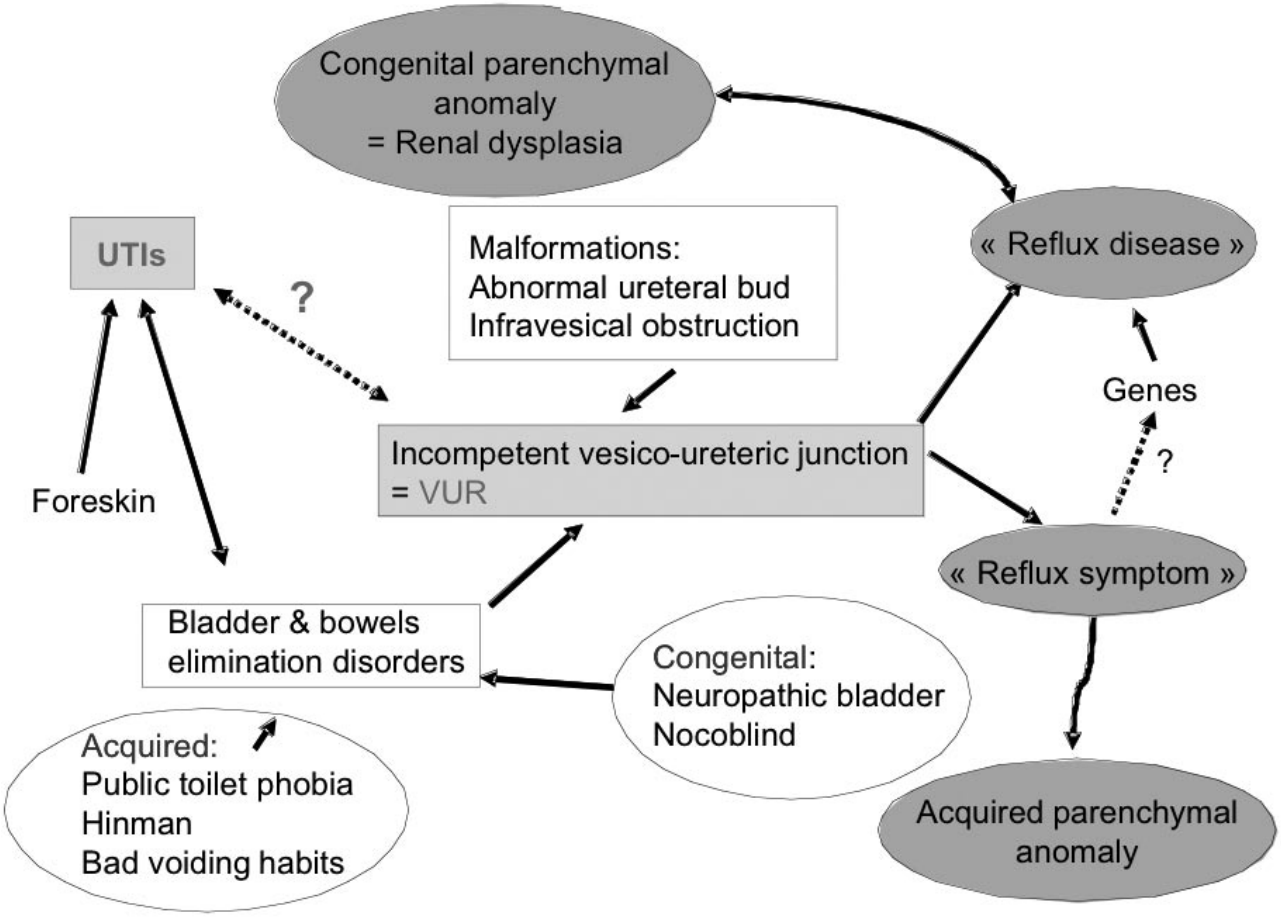

FIGURE 1.

In older children

A strong correlation exists between bladder dysfunction, such as instability and dyssynergia, and UTI which are found together in 60% of cases, as well as with VUR in 20%. It clearly predominates in female patients (19) (III/B). This dysfunctional voiding patterns correlate with persistent VUR and UTI, regardless of surgery (20) (III/B). This is highly suggestive of an acquired form of VUR of low grade with no dilatation of the urinary tract, which is predominant in female patients.

When to look for VUR?

Prenatal dilatation

Fifteen percent of prenatal urinary tract dilatations are found related to VUR on postnatal cystography (Dhillon J and Ransley PG, personal communication) (21). Severe VUR is associated with bilateral dilatation and congenital renal damage (60%), and predominates in males (75% of all), with lower rates of spontaneous resolution (50%) (4) (III/B). Moreover, there is a significant correlation between antenatal degree of dilatation and incidence of VUR. However a normal prenatal renal sonography does not exclude VUR (22) (III/B).

Febrile urinary tract infection

After a first episode of febrile UTI, VUR is found in 40% on cases (7) (IIb/B). Therefore, VUR probably needs to be investigated if one assumes that antibioprophylaxis may reduce recurrence of UTIs and subsequent renal scarring.

Siblings

The incidence of VUR in siblings is as high as 34% (23) (III/B). Siblings have VUR of low grades (98%), a low risk of renal damage (11%), and are asymptomatic in 50% of cases (24) (IIb/B). One could discuss the use of isotopic studies as a screening test, but it does not appear to be beneficial, since 9 negative DMSA scans are necessary to detect 1 VUR with renal damage (25) (III/B). Moreover, there is no evident benefit that screening and giving antibioprophylaxis in asymptomatic siblings decreases post-infectious renal anomalies.

Other uropathies

Many paediatric urologists look for VUR when another urological pathology is found such as dilated upper urinary tracts, urine flow impairments, bladder outlet obstruction, multicystic renal disease or neuropathic bladder, because of their frequent association with VUR. There is however no evidence other than experience in common practice that this screening is beneficial in term of infection and renal protection. In the light of these data, VUR should be investigated in the 3 first situations, and discussed in the last 2 clinical presentations.

How should we look for VUR?

Conventional contrast cystography

Conventional cystography is the standard positive diagnostic investigation despite its radiations and discomfort. Its specificity is high and it gives information about the anatomy of upper and lower urinary tract. However, its sensitivity is low, as VUR can be shown in 20% after a previous negative cystography (26) (IIb/B).

The evidence and grade of VUR is not influenced by timing, whether cystography is performed 1 week or more after symptomatic UTI (27) (IIb/B).

UTI is a complication of urethral catheterization in up to 20% (28) (III/B) although in most specialized units, it is found in 1% of all paediatric cystographies. Other rare complications include dysuria and perineal discomfort, hypersensitivity reactions, perforation of the bladder, malposition of catheters, and most of all radiations (29).

Several recent studies discuss the benefit of a micturating cystogram in the investigation of a first UTI. When the renal sonography is normal, the cystography should be reserved for those cases where an abnormal DMSA scan is found or if surgery is contemplated. When the renal sonography is abnormal, a cystography should be performed in all infants irrespective of the findings of the DMSA scan (III/B) (30)).

Nuclear cystography

The main pros of direct nuclear cystography compared to conventional contrast cystography are its much higher sensitivity (91% versus 45% respectively (31) (IIb/B) because of continuous imaging, and its lower radiation exposure. However, this technique fails to give anatomical information about the upper tract, and the urethra in males. Its most valuable contributions are the evaluation of female patients with normal ultrasound scans, and the follow up of VUR managed medically.

Indirect isotopic cystography using Mag 3 has poor records to detect reflux especially in low grades VUR although it has the advantage to avoid urethral catheterization (32) (IIb/B). Moreover, 15% of false positive VUR is reported (33) (III/B), making this technique rather poorly accurate.

Ultrasonography

Ultrasound scanning is inadequate for the positive diagnosis of VUR: its sensitivity is 10% and the positive predictive value 40% in the detection of VUR after the occurrence of febrile UTI (7) (IIb/B). There is no correlation between sonography, and existence or "severity" of VUR associated to UTI (34) (III/B). Fifteen percent of prenatal upper urinary tract dilations are related to VUR. Moreover, 25% of renal units in children who had prenatal diagnosis and VUR confirmed postnatally, including "high grade" VUR, are normal on postnatal sonography (35) (III/B). The best timing to perform the first postnatal sonography is between day 7 to 10, because earlier evaluation usually underestimates the severity of dilatation (36) (III/B). However, it is appropriate to perform ultrasound scan earlier in selected cases such as posterior urethral valves in boys.

Sonography has also a bad accuracy for the detection of renal anomalies, with a sensitivity between 37 to 100% when compared to DMSA (37) (IIb/B).

Ultrasound dilatation may be a relevant prognosis parameter as the degree of sonographic dilatation correlated well with the grade of reflux, and partially resolved after surgical correction (38) (III/B). VUR associated

with ultrasound dilatation of the upper tract correspond to high grade and malformative VUR. However, absence of dilatation does not exclude high gradeVUR, i.e. positive predictive value is good, while negative predictive value is poor for high grade VUR.

DMSA renal isotopic scan

DMSA scan is the gold standard study for renal damage in VUR (39) (IIb/B), with a sensitivity of 100% and a specificity of 80% (40).

DMSA should be performed 6 months after a febrile UTI, since 83% of acute lesions on initial DMSA during PNA improve or disappear (41) (III/B).

Other common investigations

Complications found with VUR such as hypertension and renal failure should be systematically assessed, considering the significant statistical association between renal lesions and VUR. Current practice is to look for hypertension and tubular damage in all children presenting with renal lesions. In the majority of cases, assessment of bladder and intestinal behaviour including history, uroflowmetry, post-voiding residue and bladder wall ultrasound assessment, are sufficient to distinguish dysfunctional from malformative VUR. Abdominal plain X-ray is commonly used in the assessment of constipation (42) (IIa/B), and may identify incidental anomalies (vertebra, stones). In some cases, urodynamic studies can be useful (18) (IIa/B), especially if a radical treatment of VUR is considered. Even if evidence level is low, etiologic diagnosis of VUR is crucial to choose the most adequate treatment.

High serum procalcitonin seems to be a stong predictor of VUR in children with a first febrile urinary tract infection, with a sensitivity rate of 75% for all-grade VUR, 100% for grade 4 or 5, but with a specificity rate of 43% (III/B) (43).

Should we treat VUR?

Several data report high rates of spontaneous resolution of VUR. Normal DMSA, normal bladder function and no upper tract dilatation are good predicting factors for spontaneous resolution (100% compared to 30% if kidneys are abnormal on DMSA) (44-45) (IIb/B).

Low grade VUR are mostly associated with bladder dysfunction, while high grade VUR are essentially malformative and more prone to radical treatments.

How should we treat reflux?

Antibioprophylaxis

No publications document that antibioprophylaxis prevents UTI with or without VUR (46) (Ia/A). The current attitude of giving antibioprophylaxis to all children with VUR is based on the fact that prophylaxis reduces the incidence of renal scars after pyelonephritis (5) (III/B).

A recent prospective randomized study shows that antibiotic prophylaxis did not reduce the incidence of UTI in young children with low grade RVU, but it may prevent pyelonephritis in boys with grade III RVU (47)(II/B).

Adverse effects are reported to be low (10%) and benign, i.e. nausea and vomiting for nitrofurantoin, and skin reactions or minor bowel disorders for sulfonamides leading to discontinuation in 8% of cases (48) (III/B). Mutagenic effect (in mice) of nitrofurantoin in experimental studies led to its withdrawal in some countries (49). It is also possible that putting children on a long term prophylaxis exacerbates antibiotic resistance.

There is no difference between medical and surgical treatment (50-51) (IIb/B), in terms of risk of UTI, and reduction in risk of new or progressive renal anomalies on imaging studies. This finding is extended to somatic and renal growth, renal function, and concentrating ability at 10 years (52-54) (IIb/B).

However, the timing of antibiotic discontinuation is a question of empirical preferences. Some prefer to wait until the age of 7-8 years, while others wait until the age of toilet training. Some choose to stop antibioprophylaxis in asymptomatic children after a certain age. A consensus exists on the fact that any symptomatic UTI should be immediately treated by adequate antibiotics without delay. If the appropriate treatment is postponed, renal damage may occur (55) (III/B).

Surgery

The only advantage of surgery versus medical treatment is a significant decrease in the incidence of pyelonephritis, but it does not reduce the number of UTIs neither renal damage (acquired or progressive) (56) (IIb/B).

In the hands of experienced surgeons, ureteral reimplantation stops VUR in 98% (57) (III/B).

Postoperative morbidity mainly includes ureterovesical obstruction or persistent VUR which can lead to renal damage. The non recognition of the pathophysiology of VUR is one element which may explain some surgical failures. Contralateral VUR appearing after correction of unilateral reflux has also been reported in 4.6% of cases, but usually resolves with time (58) (IIb/B). Transient urine retention, fluid collections, and infection can also complicate this surgery.

Long-term follow-up studies up to 20 years confirm the ongoing risk of UTI including febrile UTIs (46-52%) (59) (III/B), as well as the development of hypertension (6%) and renal anomalies (20%) despite successful surgery (60) (III/B).

Cystoscopic subureteral injection

"Five years of antibiotics or one endoscopic injection?"… or no treatment at all! As the best results of injection are found with low grade VUR which tends to resolve with growth and maturation of the bladder in most cases, the question of the indications for injection needs to be addressed.

The success rate of endoscopic treatment is significantly lower, 80.6 to 91% (61) (III/B). In addition, there is a potential risk of migration and toxicity of some "biocompatible" bulking agent used, as well as a risk of ureteral obstruction and recurrence of reflux with this technique.

CONCLUSION

Most of our believes and managements concerning reflux are based on low evidence publications. Does it imply that the rationale behind our decisions is weak, or does it mean that EBM is an inappropriate exercise in many topics of medicine? There is very low evidence that EBM is an acceptable method to evaluate our current management of most diseases (62-63) (Ia/A).

Nevertheless the search for VUR seems to be justified for prenatal urinary tract dilatation and FUTI. Surgery is the treatment of choice when recurrent infections and deterioration of renal function occur. There is however no consensus regarding persistent asymptomatic VUR, indication and duration of antibioprophylaxis and the choice of radical treatment, which is still dependent on each individual convictions.

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