Original Article

Predict the spontaneous resolution of vesicoureteral reflux by direct radionuclide cystography

C. Hu a, N.-J. Peng a,b,1, H.-S. Lin a, Y.-H. Chiou b,c, ∗

a Department of Nuclear Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
b National Yang-Ming University, Taipei, Taiwan
c Division of Pediatric Nephrology, Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

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A B S T R A C T

Objectives: To evaluate the prognostic value of initial direct radionuclide cystography (DRC) for spontaneous resolution of vesicoureteral reflux (VUR).
Methods: Fifty-one children with initial diagnosis and 1–6 years’ follow-up of VUR by DRC were enrolled in this study. VUR was graded according to the anatomic grading as (1) mild reflux corresponding to tracer just in ureter, (2) moderate reflux with accumulation of activity in a non-dilated collecting system and ureter, and (3) severe reflux equated with a dilated ureter and collecting system. The severity of VUR was also expressed according to the functional classification as (1) transient reflux, which occurred at filling or voiding phase only and (2) persistent reflux, present in both filling and voiding phases.
Results: Twenty-nine of the 51 children had unilateral VUR, and the other 22 had bilateral VUR. In the total of 73 refluxing ureters, there were 12 mild, 49 moderate and 12 severe VUR according to anatomic grading, and 30 transient and 43 persistent VUR according to the functional grading. After follow-up, resolution of VUR was found in 92% (11/12) of mild, 59% (29/49) of moderate and 25% (3/12) of severe VUR (P = 0.04, mild vs. moderate; P = 0.003, mild vs. severe). Eighty percent (24/30) of transient and 44% (19/43) of persistent reflux showed spontaneous resolution (P = 0.003).
Conclusions: DRC allows anatomic and functional classification of VUR. It is an ideal method for the diagnosis, staging and follow-up of VUR, and provides valuable information to predict the patient’s outcome.

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Previsión de la resolución espontánea del refluo vesicoureteral mediante cistografía isotópica directa

R E S U M E N

Objetivos: Evaluar el valor pronóstico de una cistografía isotópica directa (CID) inicial para la resolución espontánea de refluo vesicoureteral (RVU).
Métodos: Se incluyeron 51 niños con un diagnóstico inicial y con 1 a 6 años de seguimiento de RVU mediante CID. Los RVU fueron clasificados según los grados anatómicos de la manera siguiente: (1) refluo leve que corresponde a trazador solamente en el uréter, (2) refluo moderado con acumulación de actividad en un sistema colector sin dilatar y uréter, y (3) refluo severo con un uréter y sistema colector dilatados. La severidad del RVU también se expresó según la clasificación funcional como: (1) refluo transitorio, que ocurre solo en la fase de llenado o vaciado, y (2) refluo persistente, presente tanto en las fases de llenado como de vaciado.
Resultados: Veintiocho de los 51 niños presentaron RVU unilateral y los otros 22 tuvieron RVU bilateral. De los 73 uréteres con refluo, hubo 12 con RVU leves, 49 moderados y 12 severos, según la clasificación anatómica, y 30 transitorios y 43 persistentes según la clasificación funcional. Después del seguimiento, se observó resolución de RVU en el 92% (11/12) de los leves, en el 59% (29/49) de los moderados y en el 25% (3/12) de los severos (p = 0.04, leve vs moderado; p = 0.003, leve vs severo). El 80% (24/30) de los reflujos transitorios y el 44% (19/43) de los persistentes demostraron resolución espontánea (p = 0.003).
Conclusiones: Una CID hace posible la clasificación anatómica y funcional del RVU. Es un método idóneo para el diagnóstico, estadificación y seguimiento de RVU, y proporciona información valiosa para predecir el resultado del paciente.

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* Corresponding author.
E-mail address: yhchiou@vghs.gov.tw (Y.-H. Chiou).
1 Co-1st author.

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Introduction

Vesicoureteral reflux (VUR) is one of the most common diseases in infancy and childhood that affects approximately 1–2% of all children. About one third (25–40%) of the children who have urinary tract infection (UTI) are accompanied with the presence of VUR. The principal long term consequence of VUR, particularly when associated with infection, is the development of acute pyelonephritis (APN), which may lead to serious renal sequelae, such as renal scarring, hypertension and chronic renal failure.

Early investigation of VUR is essential for the accurate assessment of pathology and hence appropriate management to prevent progression to renal parenchymal damage. Radiographic voiding cystourethrogram (VCUG), the fluoroscopic contrast X-ray of bladder and lower urinary tract, has been frequently used for detection of VUR. It can provide detailed anatomic information for the definition of VUR, but its high radiation limits the availability of continuous monitoring and close follow-up. Direct radionuclide cystography (DRC) has gained increasing acceptance as a useful method to detect VUR during the past several years. It is shown to be more accurate than VCUG for the diagnosis of VUR in children and provide better sensitivity, especially in detecting transient reflux.

Because of its safety, high sensitivity and minimal radiation exposure, DRC has been suggested for the initial diagnosis and follow-up of VUR.

There are two ways to treat VUR. Children can receive non-invasive medical treatment with a regimen of long-term antibiotic prophylaxis to prevent UTI and renal damage till the spontaneous resolution as they grow up. Surgical treatment of VUR offers an invasive but immediate correction of the anatomic problem and is often recommended in children with recurrent UTI despite antibiotic prophylaxis, especially in high grade VUR. Since there is still difficulty in making a decision for optimal treatment, we hope to predict the prognosis at initial diagnosis of VUR, and offer a better therapeutic strategy as soon as possible. Therefore, the aim of the study was to evaluate the prognostic value of initial DRC for spontaneous resolution of VUR.

Materials and methods

Patients

Eight hundred and thirty-eight children were referred to our department for initial DRC due to various urinary tract diseases (mostly UTI). VUR was diagnosed in 135 of them (16%). In our hospital, the goal of treatment for VUR was to prevent kidney damage, and the plan of treatment was made according to severity of reflux, breakthrough infection and patient age. Therefore, antibacterial prophylaxis with a yearly DRC follow-up was the first choice for children with mild to moderate VUR because it was more likely to resolve spontaneously. Surgical correction was indicated in children with breakthrough infection and those with severe VUR older than 1 year, since infants with severe VUR had higher resolution rate in the first year. In the 135 children with VUR, 44 underwent corrective reflux surgery soon due to congenital abnormality of ureters, severe VUR beyond infancy or breakthrough UTI despite prophylactic antibiotics. Another 40 children were lost to follow-up. Finally 51 children with VUR (including 8 infants with severe VUR) were enrolled in this study, identified with an initial DRC and on a yearly follow-up schedule. Twenty-three were boys and 28 were girls. VUR was detected at a mean age of 17 ± 20 months (range 5 days to 5 years). At the time of the first DRC, the clinical diagnosis was febrile UTI in 46 children, meningocle with neurogenic bladder in 2, prenatal hydronephrosis in 2 and choordee penile in 1. All children with VUR were given prophylactic antibiotics treatment after diagnosis and underwent a mean of 2 years (range from 1 to 6 years) of follow-up DRC. This study was approved by the Institutional Review Board and the Hospital Ethics Committee.

DRC protocol

All patients underwent Foley catheterization before the DRC. Imaging acquisition was started at the beginning of administration of 18.5 MBq (0.5 mCi) 99mTc-DTPA via indwelling catheter, and then followed by instillation of optimal amount of normal saline. The expected bladder capacity (ml) was body weight (kg) × 7 for infants and (age in years +2) × 30 for children over 1 year of age. Once the instilled saline was sufficient to fill the bladder, Foley catheter was removed and the patients were asked to void as much as possible. Sequential images were continuously recorded with the patient supine in the posterior view on a gamma camera (Siemens orbiter 75; Siemens Corp., Hoffman Estates, IC) with a low-energy, parallel-hole and all-purpose collimator in a 64 × 64 matrix at the frame rate of 15 s per image. The bladder and both kidneys were within the field of view throughout the whole course.

Image interpretation

VUR was graded anatomically as (1) mild reflux corresponding to tracer just in ureter, (2) moderate reflux that is the accumulation of activity in a non-dilated collecting system and ureter, and (3) severe reflux that is equated with a dilated ureter and collecting system. The severity of VUR was also expressed according to the functional classification as (1) transient reflux occurring at filling or voiding phase only, or (2) persistent reflux present in both filling and voiding phases.

Statistical analysis

Chi-square test was used to determine the significance of difference between groups. Differences were considered significant at P < 0.05. Cox regression curve was derived from Kaplan–Meier method. All of the calculations were performed using SPSS version 12.0 (SPSS, Chicago, IL).

Results

The initial DRC showed unilateral VUR in 29 of the 51 children and bilateral VUR in the other 22 children, making a total of 73 refluxing ureters. Anatomic grading showed 12 of them to be mild, 49 to be moderate and 12 to be severe VUR. Transient VUR according to functional classification was seen in 30 refluxing ureters (28 at voiding and 2 at filling phase) (Fig. 1), and persistent VUR in 43 refluxing ureters (Fig. 2).

The follow-up DRC showed resolution of VUR in 43 of the 73 (59%) refluxing ureters, including 11 of the 12 (92%) mild VUR, 29 of the 49 (59%) moderate VUR and 3 of the 12 (25%) severe VUR. The mean times to resolution were 12.3 months (range from 9 to 15 months) for mild VUR, 20.4 months (range from 13 to 42 months) for moderate VUR and 45.7 months (range from 35 to 55 months) for severe VUR (Fig. 3). Spontaneous resolution was obviously associated with the degree of reflux (P = 0.04, mild vs. moderate; P = 0.003, mild vs. severe). Transient VUR resolved in 24 of the 30 (80%) refluxing ureters, and persistent VUR in 19 of the 43 (44%) refluxing ureters. The mean times to resolution were 14.7 months (range from 9 to 29 months) for transient VUR and 27.0 months (range from 14 to 55 months) for persistent VUR (Fig. 4). Transient VUR was nearly twice more likely to resolve than the persistent VUR (P = 0.003). Combined analysis of anatomic and functional classification found resolution in all of the 8 mild transient VUR and only 3 of 12 severe persistent VUR (P < 0.001).
Among children with VUR, there were 23 boys and 28 girls. Spontaneous resolution was found in 10 of the 23 (43%) boys and 15 of the 28 (54%) girls ($P > 0.05$). The initial DRC showed unilateral VUR in 29 and bilateral in 22 children. Spontaneous resolution was found in 13 of the 29 (45%) unilateral and 12 of the 22 (55%) bilateral VUR ($P > 0.05$). Therefore, gender or laterality made no significant difference in spontaneous resolution rate.

**Discussion**

By reviewing of articles\textsuperscript{12–17} we have summarized two major pathogeneses of pediatric VUR with various severity, which were related to (1) congenital structural defect of urinary tract, such as wrong insertion angle of ureter, short intravesical ureter, vesicoureteral junction (VUJ) deformity or outlet obstruction by posterior urethral valve, and (2) neurogenic bladder or immature bladder function, such as temporary intravesical pressure elevation at filling phase by detrusor overactivity or voiding phase by detrusor–sphincter dysynergia. VUR has a chance of resolving spontaneously because the pathogenesis is sometimes reversible, for example, short intravesical ureter may elongate, wrong ureter insertion may change to a right angle or the function of immature bladder matures when the child grows. However, it is difficult and complex to estimate and follow these various underlying problems at routine work. Therefore, to develop a simple way for evaluating the severity of VUR is needed to predict the patient’s outcome.

In diagnosing VUR, DRC offers an extra advantage for continuously monitoring the whole micturition cycle including filling and voiding phases, in contrast with that VCUG captures only several separated voiding images restricted by high radiation exposure. The severity of VUR can be estimated functionally and physiologically by the timing reflux appears. When the valve mechanism of VUJ against intravesical pressure is serious dysfunction or absent, the reflux would occur freely during both micturition phases and result in persistent VUR, indicating a more severe state. When the VUJ is only partial dysfunction in some situations such as elevation of intravesical pressure at filling or voiding phase, the VUR would occur less freely with a shorter duration, indicating a less severe state. Therefore, persistent VUR was considered a higher grade and more resistant to spontaneous resolution than transient one.

In this study, the rate of spontaneous resolution was significantly higher in transient VUR than in persistent VUR (80% vs. 44%, $P = 0.003$). In the 30 transient refluxing ureters, 2 were present during filling phase and 28 during the voiding phase. Podesta et al. have reported detrusor overactivity during filling phase and high intravesical pressure during voiding as a transient functional abnormality of urinary tract during development of normal urine control and related to the formation of VUR,\textsuperscript{12} which may disappear as bladder function matures.\textsuperscript{13} Hinman et al. have noted that VUR occurred at low intravesical pressure was less likely to resolve spontaneously.
than that at high pressure.\textsuperscript{16} It may be the reasons why transient VUR has higher spontaneous resolution rate than persistent one as children grow up. Papachristou et al. have demonstrated in their 3-year observation that VUR occurring at a lower bladder pressure (<20 cm H\textsubscript{2}O) and a filling volume less than 45% of the total bladder volume indicate a low probability for VUR resolution.\textsuperscript{19} Mclaren et al. have reported another functional grading of VUR during bladder filling as “one-third bladder volume grades (BVG)” of low, moderate and severe BVG.\textsuperscript{20} The spontaneous resolution of continuing VUR assessed from DRC in low, moderate, high and void BVG is 40%, 66%, 74% and 64%, respectively. These studies using different parameters indicated a similar result that the VUR was less likely to resolve spontaneously if reflux appeared earlier and persisted longer. In this study, persistent VUR also showed a low spontaneous resolution rate. In comparison with the methods mentioned at prior study, the two-phase analysis of VUR by DRC is much easier. The outcome of the patient evaluated by simply visual interpretation is well correlated with other reports without the need of intravesical pressure measurement and volume calculation. The “two-phase functional VUR grading” seems to be a simple way to estimate the physiological severity and provides a prognostic value of VUR.

In conventional anatomic classification, VUR on DRC was classified according to the international system of radiographic grading of VUR to 3 grades as mild in grade I, moderate in grade II, and severe in grade IV, V due to less anatomic resolution of DRC in comparison with VCUG.\textsuperscript{11} In Arant et al’s report, spontaneous resolution rate after 5 year follow-up in infants and young children with primary VUR was 82% in grade I, 80% in grade II and 46% in grade III refluxing ureters.\textsuperscript{21} In another study of patients with prenatal hydronephrosis, there was resolution in 81% of grade I-III and 38% of grade IV, V refluxing ureters.\textsuperscript{3} Our study showed resolution of VUR in 92% of mild, 59% of moderate and 25% of severe refluxing ureters. The frequency of spontaneous resolution of VUR decreased as the anatomic grade of reflux increased, in agreement with the Schwab et al. study in which the annual spontaneous resolution rate in the initial 5 years was 13% in grade I–III and 5% in grade IV, V.\textsuperscript{22} A recent retrospective study reviewed the outcome of 2462 patients with primary VUR diagnosed between 1998 and 2006. It showed that spontaneous resolution of VUR in 1257 patients (51%) at a mean duration of two years and the rates of spontaneous resolution be 72%, 81%, 49% and 32% for Grades I, II, III, and IV/V, respectively.\textsuperscript{23} The overall 59% resolution rate in our study was also comparable with the prior studies (53–68%).\textsuperscript{20–22}

Our results showed that in the refluxing ureters of the same anatomic grade, transient VUR had a higher spontaneous resolution rate than persistent VUR. In the same functional grade of VUR, the spontaneous resolution rate decreased as the anatomic grade increased. Combined analysis of anatomic and functional classification found all of the 8 mild transient VUR to resolve in the follow-up period, compared with only 3 of 12 severe persistent VUR that made it ($P<0.001$). The present findings may suggest that the anatomic and functional characteristics are both prognostic factors related to the resolution of VUR. When anatomic and functional grades of VUR are both increased, VUJ is likely to lose more function so that the VUR appears earlier, persists longer, refluxes to a higher level of urinary tract and resolves harder.

Some other factors are reported to relate to resolution of VUR, such as age, gender, recurrent UTI and bladder dysfunction.\textsuperscript{9,10,21} Sjostrum et al. have reported that a high spontaneous resolution rate of grades IV and V refluxes (29%) in male infants.\textsuperscript{10} In this study, however, gender or laterality made little difference in the spontaneous resolution of VUR.

Some pitfalls may lead to a potential selection bias in this study. First, in our hospital, children with severe VUR older than 1 year underwent corrective reflux surgery soon after diagnosis instead of conservative antibacterial prophylaxis for fear that low spontaneous resolution rate may cause permanent renal damage.\textsuperscript{10} Thus, all cases with severe VUR in this study were infants. Second, 40 of the 135 children with VUR were lost to follow-up. Some parents may hesitate to have their kids receiving DRC just for follow-up. Therefore, only 51 children with complete yearly follow-up were enrolled in this study. We intended to estimate the relationship between anatomic and functional VUR grades to see if they are independent to each other. However, our results did not reach statistical significance ($P>0.05$), probably due to too few cases. Thus, study on larger population is mandatory to evaluate the interactions between anatomic and functional VUR grades.

**Conclusion**

In addition to the conventional anatomic classification, we developed a novel functional classification of VUR by DRC. To the best of our knowledge, no study has addressed such a simple functional classification to evaluate the prognostic value for spontaneous resolution of VUR without the need of further complementary equipment or calculation. This study has shown that higher anatomic and functional grades are both negative predictive factors for spontaneous resolution of VUR. DRC is an ideal method for the diagnosis, staging and follow-up of VUR, and provides valuable information to predict the patient’s outcome.

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**Conflict of interests**

There was no existence of conflicts of interests of each one of the authors.

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