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Urinary bladder volume and pressure at reflux as prognostic factors of vesicoureteral reflux outcome

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Abstract *Background:* Controversy exists as to whether the outcome of vesicoureteral reflux (VUR) can be prognosticated by direct radionuclide cystography (DRC).

Objective: To correlate the quantitative data obtained by DRC with disease outcome in infants with VUR and positive DRC 1 year after diagnosis. *Materials and methods:* The medical records of 109 children with known primary VUR diagnosed during the first year of life were studied retrospectively. One year after diagnosis all patients underwent DRC. Children with a positive first DRC were followed up for the next 36 months. Fisher's exact test was used to calculate the statistical significance of differences in the number of ureters with resolved reflux, as related to quantitative data obtained during the first DRC. *Results:* The first DRC, performed 1 year after the initial diagnosis, was positive in 49 children (26 with bilateral reflux). Quantitative

data derived from this first examination could not establish any prognostic value for a refluxing volume of <2% of the total vesical volume or a reflux at a bladder volume of more than 60% of total bladder capacity. When this limit was lowered to 45%, a statistically significant difference was found ($P=0.046$). Moreover, when a bladder pressure at the time of reflux of more than 20 cm H₂O was set as a criterion, an extremely significant probability value was calculated ($P=0.0009$). *Conclusions:* VUR occurring at a bladder pressure of less than 20 cm H₂O and a filling volume of less than 45% of the total bladder volume indicate a low probability for VUR resolution within the subsequent 36 months, in infants with known reflux.

Keywords Bladder · Ureter · Vesicoureteral reflux · Radionuclide cystography · Children

Introduction

Vesicoureteral reflux (VUR) is a significant predisposing factor for renal scarring, hypertension and eventual end-stage renal disease [1, 2]. The application of diagnostic imaging procedures such as radiographic voiding cystourethrography and radionuclide cystography have contributed to the earlier recognition of VUR in infants and have led to increased medical or surgical interven-

tions. It is generally accepted that this treatment will have a favourable impact on the incidence of pyelonephritis among these patients.

Radionuclide cystography is presently the investigation of choice for the follow-up of children with VUR. This method offers the advantage of lower radiation dose to the child, the capacity for continuous digital acquisition, assessment of bladder volume and pressure at the time of reflux and calculation of reflux

volume. Information considering the prognostic value of the latter digital data is controversial. It has been reported that VUR at a low grade of bladder volume is associated with resistance to spontaneous VUR resolution [3, 4] and increased renal scarring [4]. A smaller risk for surgery has been calculated for patients in whom reflux occurred when their bladder was filled to more than 60% of total bladder capacity, as well as for patients with a reflux volume of less than 2% of total bladder capacity [5]. However, other investigators using the same criteria have concluded that radionuclide cystography cannot predict outcome in patients with VUR [6].

In the present study, we retrospectively assessed the outcome of VUR in relation to quantitative data from the first radionuclide cystogram that was performed 1 year after diagnosis in children initially diagnosed before the first year of age.

Materials and methods

We retrospectively examined the medical records of 109 children (75 boys, 34 girls) with primary VUR. All patients were examined because of urinary tract infection; there were no patients with prenatal hydronephrosis or any predisposing factor for VUR. The diagnosis of VUR was first established by a radiographic cyclic voiding cystourethrogram (VCUG) in both boys and girls during the first year of life. Particular attention was given to adequate bladder filling and complete voiding during both cycles of the VCUG [7]. VUR was graded according to the classification system of the International Reflux Study Committee [8].

One year after the initial diagnosis (at age 19.2 ± 3.5 months) all children underwent direct radionuclide cystography (DRC) to evaluate progress of the condition. Infants with negative DRC were re-examined after 6–8 months in order to exclude VUR. Consequently, infants were followed-up for a period of at least 36 months thereafter (until age 65.8 ± 5.2 months). All infants received long-term antimicrobial chemoprophylaxis consisting mainly of amoxicillin or cotrimoxazole, without excluding other antibiotics as necessary. Prophylaxis was given as a single continuous dose until VUR had resolved.

Routine urinalyses and urine cultures were carried out monthly and without delay if fever and/or other symptoms developed. Haematologic tests, blood pressure measurements, DRC and renal ultrasonography (US) were carried out annually. Infants received an initial US examination and a ^{99m}Tc -DMSA renal scan that was repeated after 6 months if pyelonephritis was suspected and thereafter every 1–2 years, depending mainly on the establishment of new scars.

Cessation of VUR was considered when it was no longer demonstrable on two successive DRCs, with an interval of at least 6 months between them.

Direct radionuclide cystography

Children were aseptically catheterized with the appropriate-for-age Levine-type straight catheter. Before the onset of the study the bladder was emptied through the catheter. The administration of the radiopharmaceutical (18.5 MBq of ^{99m}Tc -pertechnetate in 10 ml of warm normal saline) was followed by gradual filling of the bladder with normal saline solution [9]. Bladder pressure was measured during the examination using a three-way system and an open, sterile communicating catheter attached to a centimetric scale, the 0 point of which was placed about 1 cm below the level of the child's abdomen. Posterior-view dynamic acquisition was obtained with a large-field-of-view gamma camera (Vision DS7, SMV International, Buc, France) using a low-energy high-sensitivity collimator. Data were acquired at 10 s/frame until the intravesical volume of saline was approximately equal to the maximum for the child's normal bladder capacity (NBC) for age according to the formula $\text{NBC (ml)} = (\text{age in years} + 2) \times 30$ [9]. A posterior view dynamic study was then obtained at 5 s/frame with a full bladder and during voiding. Two additional static views were acquired before and after voiding. Reflux volume was calculated from the prevoiding static view by measuring the counts from regions of interest (ROI) placed over the ureters, pelvis and bladder [9].

Statistical analysis

The statistical program, GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, Inc., San Diego, USA; <http://www.graphpad.com>), was used. Contingency tables were analysed using Fisher's exact test. A difference was considered significant if $P < 0.05$.

Results

The medical records of 109 children (75 boys, 34 girls) with known VUR diagnosed radiologically in the first year of life (mean 6.15 ± 3.4 months) were reviewed. US and DMSA findings indicated that 34 children (21 boys, 13 girls) had renal scars at diagnosis. VUR was bilateral in 44 boys and 23 girls. There were a total of 176 refluxing ureters. VUR resolved in 101 of these ureters after 1 year, as indicated by the first follow-up DRC.

The first follow-up DRC was positive in 25 boys (10 with bilateral reflux) and 24 girls (16 with bilateral reflux). Nineteen of these children (9 boys, 10 girls) had scars in US and/or DMSA. Records from this DRC with regard to maximum reflux urine volume were available for all 75 refluxing ureters, whereas data regarding bladder volume and bladder pressure at the time of the reflux were available for 70 ureters.

During the follow-up period of the next 36 months, VUR resolved in 27 children (19 boys, 7 with bilateral reflux; 8 girls, 5 with bilateral reflux)—a total of 39 ureters. On the other hand, VUR persisted in 22 children (6 boys, 3 with bilateral reflux; 16 girls, 11 with bilateral reflux)—a total of 36 ureters. Eight of these children (one boy, seven girls) had renal scars. There was no development of new scars during the follow-up of any of these children.

Considering the quantitative data of the first follow-up DRC, 26 (67%) of 39 ureters with reflux resolution and 23 (64%) of 36 ureters with continuing VUR had a refluxing volume of $>2\%$ of the child's total bladder capacity ($P=0.8113$) (Table 1). Considering the bladder volume at the time of reflux, 20 (56%) of the 36 ureters with continuing VUR and 19 (56%) of the 34 ureters with resolved VUR, started refluxing during the filling phase at a bladder volume of $>60\%$ of total bladder capacity or during the voiding phase in the initial DRC ($P=1.0000$). However, when this limit was lowered to 45%, a statistically significant difference was found (Table 2, $P=0.046$). Moreover, when the bladder pressure at the time of VUR at the initial DRC was considered, a highly significant statistical difference was calculated ($P=0.0009$). In this case, 12 (33%) of the 36 ureters with continuing VUR, and 25 (74%) of the 34 ureters with resolved VUR, started refluxing during the filling phase at a bladder pressure of >20 cm H₂O or during the voiding phase (Table 3).

Female gender was also associated with continuation of reflux ($P=0.0005$). The presence of scars on DMSA or US was not associated with continuation of VUR ($P=0.8152$) or with gender ($P=0.5311$).

Discussion

Information on infants with VUR, first diagnosed at an age of less than 12 months and followed up with DRC,

Table 1 Distribution of refluxing ureters on the initial DRC according to refluxing volume and presence or absence of resolution of VUR within 36 months

Refluxing volume (% of total bladder capacity)	VUR resolved	VUR not resolved
>2	26	23
<2	13	13

is limited. The spontaneous resolution rate of VUR seems to be higher in infants than in older children. A multicentre study that reported on 401 patients with VUR grade 3 or 4 included 56 infants <1 year old at diagnosis [10]. At the 1-year follow-up, resolution was reported in 14% these infants. In a more recent study that included 82 infants, a resolution rate of 51% was reported [4]. Yeung et al. [11] reported a resolution rate of 73% during the first year in 74 infants with mild reflux (grades 1–3). In our study the first-year resolution rate was 57.4%.

Considering other prognostic factors, our data indicate the female gender is associated with a continuing risk of reflux. This finding is in agreement with other researchers [12, 13]. On the other hand, renal scarring was neither associated with gender nor with continuation of VUR. These data are in agreement with previous reports indicating that the development of acute pyelonephritis is not absolutely dependent on the presence of VUR [14].

The present retrospective study attempted to evaluate possible prognostic indices derived from the data of the first follow-up DRC performed in children with VUR diagnosed in infancy. The results indicate that a bladder volume of less than 45% of total bladder capacity or a bladder pressure of less than 20 cm H₂O at the time of reflux initiation, indicates a high probability for continuation of VUR after 3 years. We believe this is the first study that has considered bladder pressure at the time when VUR appears, which in turn appears to be a prognostic factor for reflux resolution.

Considering bladder volume at the time of reflux, the present data are consistent with a recent study on infants

Table 2 Distribution of refluxing ureters on the initial DRC according to bladder volume at the time of reflux and presence or absence of resolution of reflux within 36 months

Bladder volume (% of total bladder capacity)	VUR resolved	VUR not resolved
>45	30	24
<45	4	12
>60	19	20
<60	15	16
>80	9	6
<80	25	30

Table 3 Distribution of refluxing ureters on the initial DRC according to bladder pressure at the time of reflux and the presence or absence of resolution of reflux within 36 months

Refluxing pressure (cm H ₂ O)	VUR resolved	VUR not resolved
>20	25	12
<20	9	24

with VUR that concluded that low bladder volume at the time of reflux is associated with resistance to natural resolution [4].

Our data are also in agreement with a previous study that reported that the prognostic criteria proposed by Mosley et al. [5] (reflux volume > 2% or bladder volume at the time of reflux < 60%) cannot predict the outcome of VUR [6]. Unfortunately, it remains unknown how many children diagnosed prior to 1 year of age were

involved in the latter study. It should also be noted that our study included a different age group than the study by Mosley et al. [5], and therefore the data are not directly comparable.

In conclusion, we have shown that in children with VUR diagnosed during infancy, quantitative data, such as the bladder pressure and volume at the time of reflux, can provide significant prognostic information considering the resolution of VUR.

References

1. Olbing H, Claesson I, Ebel KD, et al (1992) Renal scars and parenchymal thinning in children with vesicoureteral reflux: a 5-year report of the International Reflux Study in children (European branch). *J Urol* 148:1653–1656
2. Smellie J, Prescod N, Shaw P, et al (1998) Childhood reflux and urinary infection: a follow-up of 10–41 years in 226 adults. *Pediatr Nephrol* 12:727–736
3. Nasrallah PF, Conway JJ, King LR, et al (1978) Quantitative nuclear cystogram: aid in determining spontaneous resolution of vesicoureteral reflux. *Urology* 12:654
4. McLaren CJ, Simpson ET (2002) Vesicoureteric reflux in the young infant with follow-up direct radionuclide cystograms: the medical and surgical outcome at 5 years old. *Br J Urol Int* 90:721–724
5. Mosley DP, Heyman S, Duckett JW, et al (1994) Direct vesicoureteral scintigraphy: quantifying early outcome predictors in children with primary reflux. *J Nucl Med* 35:1602–1608
6. Bathold JS, Martin-Crespo R, Kryger JV, et al (1999) Quantitative nuclear cystography does not predict outcome in patients with primary vesicoureteral reflux. *J Urol* 162:1193–1196
7. Papadopoulou F, Efremidis SC, Economou A, et al (2002) Cyclic voiding cystourethrography: Is vesicoureteral reflux missed with standard voiding cystourethrography? *Eur Radiol* 12:666–670
8. Lebowitz RL, Obling H, Parkkulainen KV, et al (1985) International Reflux Study in Children. *Pediatr Radiol* 15:105–109
9. Mandel GA, Egli DF, Hershey MS, et al (1999) Society of Nuclear Medicine. Procedure guideline for radionuclide cystography in children. In: *Procedure guidelines manual 1999*, Commission of health policy and practice, guidelines and communications committee. Society of Nuclear Medicine, Reston, pp 145–150
10. Tamminen-Möbius T, Brunier E, Ebel KD, et al (1992) Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. International reflux study in children. *J Urol* 148:1662–1666
11. Yeung CK, Godley ML, Dhillon HK, et al (1997) The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. *Br J Urol* 80:319–327
12. Lankanke K, Sager M, Giger A, et al (2003) Implementation of recommendations in the diagnosis of vesicoureteric reflux after urinary tract infections in Swiss children. *Swiss Med Wkly* 133:385–387
13. Marra G, Oppezzo C, Barberis V, et al (2003) Age at diagnosis of vesicoureteric reflux after urinary infection; historical changes. *Acta Paediatr Scand* 92:734–736
14. Tepmongkol S, Chotipanich C, Sirisalipoach S, et al (2002) Relationship between vesicoureteral reflux and renal cortical scar development in Thai children: the significance of renal cortical scintigraphy and direct radionuclide cystography. *J Med Assoc Thai* 85:S203–S209