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Echo-enhanced ultrasound voiding cystography in children: a new approach

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Abstract The development of echo-enhancing agents has significantly improved the detection of the movement of fluid within the urinary tract by ultrasonography (US). The purpose of our study was to compare ultrasound voiding cystography (USVC) for the detection of vesicoureteric reflux (VUR) in children with direct radionuclide voiding cystography (DRVC). Ninety-nine children, aged 1.1–12.3 years, with 198 potentially refluxing units, were investigated simultaneously by DRVC and USVC. The indications for cystography were urinary tract infection, follow-up of a previously detected VUR, and screening of siblings of children with VUR. During the investigation an echo-enhancing agent (Levovist) was administered intravesically through a catheter already in place for the DRVC. The movement of both agents, radiotracer and Levovist, was registered simultaneously by a computerized gamma camera and US, respectively. The results were analyzed with DRVC representing the reference diagnostic test. The overall sensitivity and specificity of USVC for the detection of VUR were 79% and 92%, respectively. USVC may represent a reliable diagnostic tool for the detection and follow-up of VUR in children.

Key words Ultrasound voiding cystography · Vesicoureteric reflux · Urinary tract infection

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Introduction

It is generally accepted that imaging of the upper and lower urinary tracts should be performed in all children after their first urinary tract infection (UTI). The rationale for this approach is to identify those children who may be at risk of chronic renal damage. Vesicoureteric reflux (VUR) is the most-common abnormality of the urinary tract in these children [1–3], and is also frequently detected in asymptomatic siblings of children with VUR [4]. Two methods are routinely used to identify VUR, namely X-ray voiding cystourethrography (VCUG) and direct radionuclide voiding cystography (DRVC) [5]. However, both techniques involve exposure to ionizing radiation.

Twenty years ago, Tremewan et al. [6] reported the use of ultrasonography in four adult patients with high-grade VUR. Improved techniques were reported using air-filled microspheres contained either in a contrast medium [7, 8] or in a saline solution [9]. Due to their acoustic properties, these air-filled microbubbles rendered the urine echogenic and therefore suitable for visualization on a B-mode scan. Several generations of echo-enhancing agents have been developed since, each new generation containing smaller and more-stable microbubbles. The recent development of these commercially available echo-enhancing agents has markedly improved the sonographic detection of fluid movement within the urinary tract [10]. The use of echo-enhanced renal sonography for the detection of VUR in children has already been successfully investigated in clinical trials [11–13]. The purpose of our prospective study was to determine the value of USVC for the detection of VUR in children compared with DRVC.

Materials and methods

Ninety-nine children, aged 1.1–12.3 years (mean 4.6 years), were evaluated from November 1997 to April 1998. There were 78 girls and 21 boys. USVC was performed at the same time as DRVC in

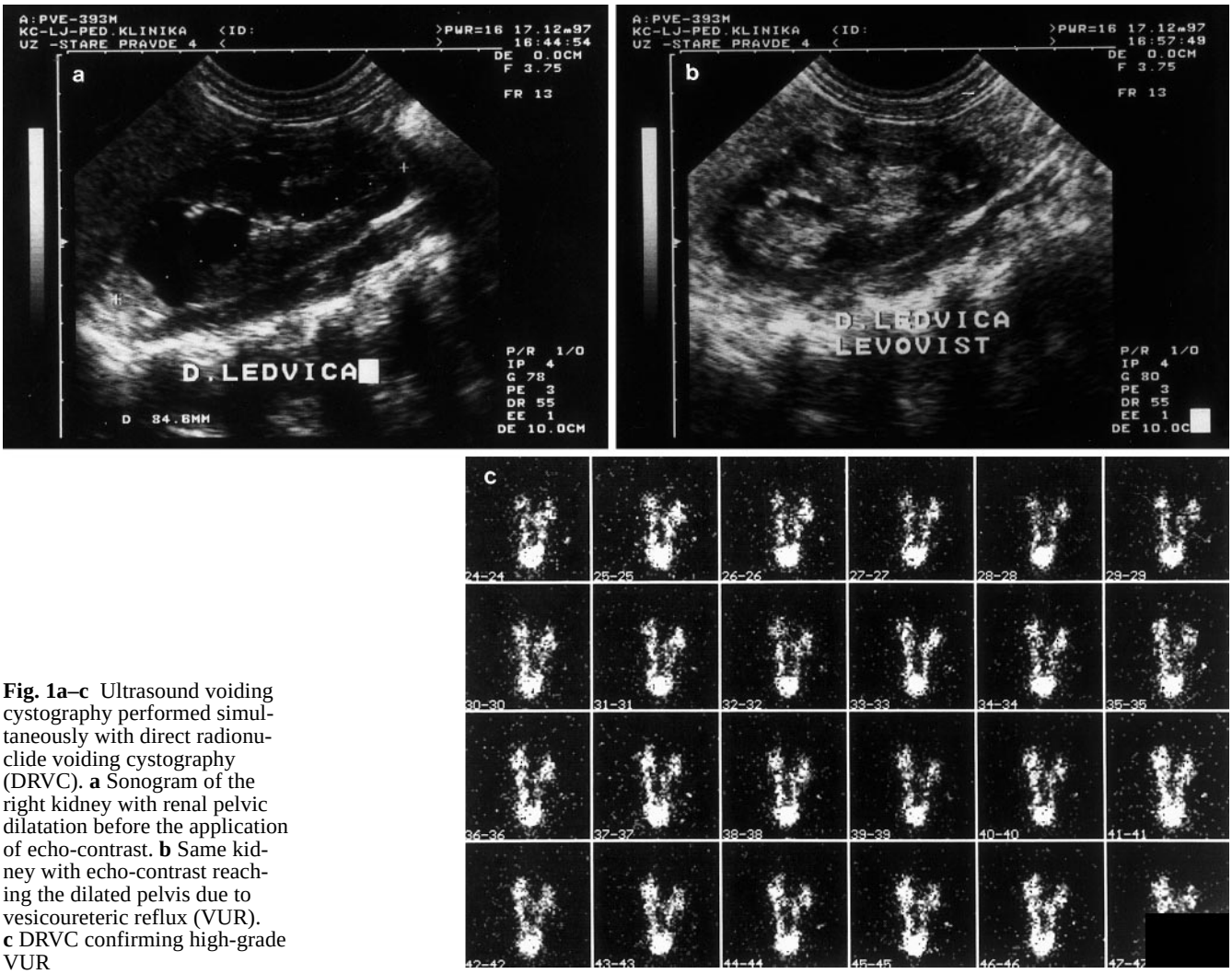

Fig. 1a–c Ultrasound voiding cystography performed simultaneously with direct radionuclide voiding cystography (DRVC). **a** Sonogram of the right kidney with renal pelvic dilatation before the application of echo-contrast. **b** Same kidney with echo-contrast reaching the dilated pelvis due to vesicoureteric reflux (VUR). **c** DRVC confirming high-grade VUR

all children. The indications for cystography were UTI, follow-up of a previously detected VUR, or screening of siblings of children with VUR. The study was approved by the appropriate medical ethics committee and written informed consent was obtained from all parents.

Radionuclide voiding cystography

The investigation was performed with the child lying supine on a transparent examination table. A narrow aspiration catheter was inserted into the urinary bladder under aseptic conditions and the urine was allowed to drain. Thereafter, the bladder was filled slowly with 20 MBq of technetium-99 m pertechnetate-labelled colloid in 250 ml of saline solution under hydrostatic pressure (40–70 cm H_2O). All the fluids used for instillation into the bladder were maintained at body temperature. When the predicted bladder volume was reached or when the child began to show signs of urge to void, an echo-enhancing agent (Levovist) was administered intravesically through the same catheter, using a three-way stopcock. The child was asked to void. Younger, uncooperative children were allowed to void spontaneously. The distribution of the radiotracer was recorded continuously by a computerized gamma camera (Siemens Basicam) with a multi-purpose collimator lying underneath the examination table, at a rate of one frame per 5 s and stored in the form of dynamic serial images. The procedure continued until the bladder was completely empty. At the end of the investigation, the data were reviewed with image enhancement. The results were evaluated separately by two independent observers blinded to the results of USVC.

Since each kidney represented an isolated potentially refluxing unit, VUR was not classified as unilateral or bilateral. It was graded as follows:

⇒ VUR grade I: radiotracer reaching the ureter only,
⇒ VUR grade II: radiotracer reaching the pelvis,
⇒ VUR grade III: radiotracer reaching the pelvis, which seemed dilated.

Ultrasound voiding cystography

The investigation was performed using a real-time scanner Toshiba SSA-240A with a 3.7-MHz and a 7-MHz transducer. The echo-enhancing agent used was Levovist [14]. Levovist consists of 99.9% microcrystalline galactose microparticles and 0.1% palmitinic acid. By adding water and agitating, a milky suspension is obtained containing air-filled microbubbles. The microbubbles are either adsorbed onto the surface of galactose microparticles or float freely in the suspension. They are covered with a thin film of palmitinic acid, which renders them more stable. A Levovist concentration of 300 mg/ml of suspension was used. The amount of suspension administered to a child was equivalent to approximately 5% of the estimated bladder volume, which was calculated according to the weight and age of the child.

Table 1 Comparison of ultrasound voiding cystography (*USVC*) and direct radionuclide voiding cystography (*DRVC*) for all grades of vesicoureteric reflux (*VUR*)

	USVC +	USVC –	Total
DRVC +	50	13	63
DRVC –	11	124	135
Total	61	137	198

Table 2 Comparison of USVC and DRVC according to grade of VUR

DRVC – grade of VUR	USVC – grade of VUR				
	0	I	II	III	Total
0	124	5	6		135
I	1				1
II	12		16	1	29
III			7	26	33
Total	137	5	29	27	198

A base-line US image of the urinary tract was obtained and the kidneys were evaluated through the ventral and dorsal approach. DRVC was then started as described above with the child lying supine on the examination table. When the predicted bladder volume was reached or when the child began to show signs of urge to void, Levovist was administered intravesically through the same catheter using a three-way stopcock. A small amount of Levovist was injected slowly at first, since too hasty filling of the bladder would cause acoustic shadowing covering the retrovesical parts of the ureters. At this time the bladder and the proximal parts of the ureters were examined. The rest of the Levovist was then administered. While awaiting micturition, the kidneys were again scanned ventrally and dorsally in longitudinal and transverse sections. The child was asked to void. Younger, uncooperative children were allowed to void spontaneously. The procedure was continued until voiding was complete. VUR was identified when hyperechogenic microbubbles were detected in the ureter and/or the renal pelvis. The person performing USVC and assessing the grade of VUR was not acquainted with the results of DRVC. The same grading scale was used as for DRVC. The prepared solution of the echo-contrast was stable throughout the procedure, which lasted about 20–30 min. All children received oral trimethoprim/sulfamethoxazole for 3 days to prevent UTI after catheterization.

Results

The results of USVC were compared with the reference method of DRVC. During the study 99 children were evaluated, contributing 198 potentially refluxing renal units. According to DRVC, reflux was present in 63 (32%) renal units. Table 1 shows the ratio between positive and negative results of DRVC and USVC. The sensitivity of USVC for the detection of VUR, regardless of the grade of VUR, was 79% and the specificity 92%.

In Table 2, the results are presented according to the grade of VUR. The most-accurate results were obtained with VUR grade III. All the 33 refluxing units were identified by USVC either as VUR grade II or grade III. All 27 cases of VUR grade III detected by USVC were confirmed by DRVC, 26 cases as VUR grade III and 1 as VUR grade II.

Discussion

All published reports of USVC compare the results with those obtained by VCUG or some form of radionuclide voiding cystography, performed either prior to or after USVC, and in some cases even several years apart [8, 9, 11, 12]. Kessler and Altman [7] performed USVC at the same time as VCUG, but because of technical difficulties only during the phase of bladder filling. Moreover, the investigators used different echo-enhancing agents, which makes the comparison of methods even less reliable. In more-recent studies both investigations were preformed during the same session, but not simultaneously [12, 13].

In our study, both investigations were carried out simultaneously, during the same procedure, and therefore the same conditions applied. We believe that this is the most-appropriate way to compare the two different methods used to detect VUR. There were several reasons for choosing DRVC, rather than VCUG, as the reference method. USVC is technically easier to perform at the same time as DRVC than VCUG. Furthermore, DRVC involves exposure to lower doses of radiation and, in skilful hands, is more sensitive than VCUG for the detection of VUR. Nevertheless, some difficulties can arise in interpreting low-grade VUR by DRVC, especially in small children. For this reason there might have been some misinterpretation of low-grade VUR (grade I-II) by DRVC, although we excluded children less than 1 year of age from our study. Since the results of DRVC were used as a reference to define the presence or absence of VUR, some cases could have been labelled as false-negative results of USVC, rather than false-positive results of DRVC. This may explain the relatively low overall sensitivity of USVC (79%) in our series. However, it is encouraging that the results of both imaging modalities (DRVC and USVC) were highly concordant when VUR of higher grades was involved. It is also noteworthy that the overall specificity of USVC for the detection of VUR was high (92%).

In conclusion, our results suggest that, in expert hands, USVC could be a reliable method for detecting and following VUR in children. By introducing an echo-enhancing agent into the bladder during routine US of the urinary tract after UTI, important information regarding VUR can be obtained. To date this additional information could only have been obtained by further radiological or radionuclide investigation. However, more data are needed before the role of USVC in detecting VUR can be defined.

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References

1. Kenda R, Kenig T, Šilc M, Zupančič Ž (1989) Renal ultrasound and excretory urography in infants and young children with urinary tract infection. Pediatr Radiol 19:299–301
2. Leonidas JC, McCauley RGK, Klauber GC, Fretzayas AM (1985) Sonography as a substitute for excretory urography in children with urinary tract infection. AJR 144:815–819
3. Alon U, Pery M, Davidai G, Berant M (1986) Ultrasonography in the radiologic evaluation of children with urinary tract infection. Pediatrics 78:58–64
4. Kenda RB, Zupancic Ž, Fettich JJ, Meglic A (1997) A follow-up study of vesico-ureteric reflux and renal scars in asymptomatic siblings of children with reflux. Nucl Med Commun 18: 27–31
5. Fettich JJ, Kenda RB (1992) Cyclic direct radionuclide voiding cystography: increasing reliability in detecting vesicoureteral reflux in children. Pediatr Radiol 22:337–338
6. Tremewan RN, Bailey RR, Little PJ, Maling MJ, Peters TM, Tait JJ (1976) Diagnosis of gross vesico-ureteric reflux using ultrasound. Br J Urol 48:431–435
7. Kessler RM, Altman DH (1982) Real time detection of vesicoureteral reflux in children. Am J Roentgenol 138:1033–1036
8. Bergius AR, Niskanen K, Kekomäki M (1990) Detection of significant vesicoureteric reflux by ultrasound in infants and children. Z Kinderchir 45:144–145
9. Hanbury DC, Coulden RA, Farman P, Sherwood T (1990) Ultrasound cystography in the diagnosis of vesicoureteric reflux. Br J Urol 65:250–253
10. Atala A, Wible JH, Share JC, Carr MC, Retik AB, Mandell J (1993) Sonography with sonicated albumin in the detection of vesicoureteral reflux. J Urol 150:756–758
11. Kaneko K, Kuwatsuru R, Fukuda Y, Yamataka A, Yabuta K, Katayama K, Miyano T (1994) Contrast sonography for detection of vesicoureteric reflux (letter). Lancet 344:687
12. Bosio M (1998) Cystosonography with echocontrast: a new imaging modality to detect vesicoureteric reflux in children. Pediatr Radiol 28:250–255
13. Darge K, Duetting T, Zieger B, Mohring K, Rohrschneider W, Troeger J (1998) Diagnosis of vesicoureteral reflux with echo-enhanced micturition urosonography. Radiologe 38:405–409
14. Fritzsch T, Schlief R (1995) Levovist. Drugs Fut 20:1224–1227

LITERATURE ABSTRACTS

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Corticosteroids in IgA nephropathy: a randomised controlled trial

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Background IgA nephropathy is progressive in most cases and has no established therapy. In this randomised trial, we assessed the efficacy and safety of a 6-month course of steroids in this disorder.
Methods Between July, 1987, and September, 1995, we enrolled 86 consecutive patients from seven renal units in Italy. Eligible patients had biopsy-proven IgA nephropathy, urine protein excretion of 1.0–3.5 g daily, and plasma creatinine concentrations of 133 mu mol/L (1.5 mg/dL) or less. Patients were randomly assigned either supportive therapy alone or steroid treatment (intravenous methylprednisolone Ig per day for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 months). The primary endpoint was deterioration in renal function defined as a 50% or 100% increase in plasma creatinine concentration from baseline. Analyses were by intention to treat.
Results Nine of 43 patients in the steroid group and 14 of 43 in the control group reached the primary endpoint (a 50% increase in plasma creatinine) by year 5 of follow-up (P<0.048). Factors influencing renal survival were vascular sclerosis (relative risk for 1-point increase in score 1.53, P=0.0347), female sex (0.22, P=0.0163), and steroid therapy (0.41, P=0.0439). All 43 patients assigned steroids completed the treatment without experiencing any important side-effects.
Conclusions A 6-month course of steroid treatment protected against deterioration in renal function in IgA nephropathy with no notable adverse effects during followup. An increase in urinary protein excretion could be a marker indicating the need for a second course of steroid therapy.

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Clinical and genetic heterogeneity in familial focal segmental glomerulosclerosis

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Background Familial forms of focal segmental glomerulosclerosis (FFSGS) that exhibit autosomal dominant or recessive patterns of inheritance have been described. The genetic basis of these hereditary forms of FSGS is unknown. One recent study of a kindred from Oklahoma with an autosomal dominant form of FSGS linked this disease to a region of chromosome 19q. In addition, polymorphisms in a gene in this region on chromosome 19q13 have been linked to congenital nephrotic syndrome of the Finnish type. We have ascertained and characterized a large family with autosomal dominant FFSGS (Duke 6530).
Methods Families were compared for clinical and genetic heterogeneity. To test for linkage of our family to this portion of chromosome 19, genomic DNA was isolated from 102 family members, and polymerase chain reaction was performed using eight microsatellite markers that spanned the area of interest on chromosome 19. Data were evaluated using two-point linkage analysis, multipoint analysis, and an admixture test
Results Linkage was excluded at a distance of ±5 to 10 cm for all markers tested with two-point log, of the odds of linkage (LOD) scores and from an approximate 60 cm interval in this area of chromosome 19q via multipoint analysis.
Conclusions FSGS has been called the “final common pathway” of glomerular injury, as it is a frequent pathological manifestation with diverse etiologies. This diversity likely correlates with the genetic heterogeneity that we have established. Thus, our data demonstrate that there are at least two genes responsible for this disease, and there is genetic as well as clinical heterogeneity in autosomal dominant FSGS.