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ORIGINAL ARTICLE

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Clinical course of prenatally detected primary vesicoureteral reflux

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Abstract The purpose of this study was to report the clinical course of medium-long-term follow-up of children with prenatally detected vesicoureteral reflux (VUR). Between 1986 and 2004, 53 (41 males) children with VUR detected by investigation of prenatal hydronephrosis were followed up for a mean time of 66 months (range: 6–200 months). Newborns were investigated by ultrasound, voiding cystourethrogram (VCUG) and DMSA scan. Follow-up clinical visits were performed at 6-month intervals. After 24 months patients were investigated by conventional VCUG or direct isotope cystogram. Survival analysis was performed in order to evaluate the resolution of the reflux. Differences between subgroups (mild vs moderate/severe reflux) were assessed by the two-sided log rank test. Thirty (58%) infants presented bilateral VUR, for a total of 83 renal units. There was a predominance of severe reflux (54%). Renal damage was detected in 33.7% of the units on first renal scan. There was a significant correlation between severe reflux and renal damage scars (RR=3.4, 95% confidence interval [CI], 1.4–8, p=0.002). Forty-seven patients were treated with continuous prophylaxis. One patient developed systolic hypertension. Urinary tract infection occurred in 12 (25%) children conservatively managed. VUR resolution was evaluated in 56 renal units. Spontaneous resolution was observed in 25 units (45%). At 48 months after diagnosis, 75% of the cases of mild reflux (I–III) and 37% of severe reflux (IV–V) had resolved (log-rank, 5.6, p=0.017). There was an improvement of nutritional parameters between admission and the end of follow-up. In conclusion, the clinical course of prenatally detected VUR followed up on a medium-long-term basis is relatively benign. Our study corroborates the results obtained in other series of infants with reflux that emphasized the heterogeneity of this disorder.

Keywords Fetal · Hydronephrosis · Reflux nephropathy · Urinary tract infection · Vesicoureteral reflux

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Introduction

Prenatal ultrasonography has resulted in an increase in the number of infants detected with significant asymptomatic uropathy, allowing treatment before the potential consequences of urinary tract infection (UTI). Although most cases of antenatal hydronephrosis are due to renal pelvic dilatation with partial or total obstruction, vesicoureteral reflux (VUR) is a common cause occurring in 10–15% [1,2].

The presenting features of prenatally detected VUR differ from those detected later in life, usually after urinary tract infection. In infants, there is a preponderance of males and a prevalence of dilated upper urinary tract with severe reflux [3]. In addition, several studies have shown that 20–30% of infants, most of them males, with dilating reflux presented a generalized small kidney with decreased renal function without a previous history of UTI [3, 4, 5, 6, 7, 8]. On the other hand, in older groups there is a preponderance of females with mild to moderate reflux and localized scars [9]. The recognition of VUR as a

heterogeneous disease and a marker for generalized disease of the whole urinary tract, which includes being born with renal dysplasia and predisposition to urine infection, is a first step towards a tailored diagnostic and therapeutic approach [10]. Recently, cohort studies of prenatally detected VUR have shown that clinical management is effective in the majority of cases, with a low urinary tract infection rate, normal renal growth, and no somatic growth retardation or hypertension [11,12]. In order to contribute to knowledge about the clinical course of prenatally detected primary VUR, we present here a series of cases followed on a medium-long-term basis.

Patients and methods

The present retrospective cohort study was conducted on 53 patients diagnosed with antenatal hydronephrosis and primary VUR who were referred to the Pediatric Nephrourology Unit (Hospital das Clínicas-UFMG, Belo Horizonte, Brazil) between January 1986 and May 2004. For neonates born at our institution, antibiotic prophylaxis was started on the first day of life using cephalexin at doses of 100 mg/day. All neonates were then investigated by ultrasound and voiding cystourethrography at the end of the first week of life or as soon as possible after referral [13]. When VUR was diagnosed, long-term prophylaxis was maintained and renal damage was investigated by renal scintigraphy with ^{99m} Tc-DMSA after the first 2 months of life. Starting at 2 months of age, the drug used for chemoprophylaxis was nitrofurantoin (1–2 mg/kg/day) or trimethoprim (1–2 mg/kg/day). The clinical approach consisted of full physical examination, including evaluation of growth and blood pressure performed at 6-month intervals during the first 2 years of life and yearly thereafter. Urine cultures were obtained during follow-up visits or during any febrile episode. Recurrent UTI was defined as growth of at least 100,000 CFU/ml in urine obtained by bag or a midstream sample, with fever (38.0°C or more) or urinary symptoms. Plasma creatinine was determined on the occasion of the postnatal examination and yearly thereafter. Glomerular filtration rate was estimated by the method of Schwartz et al. [14]. Blood pressure measurements were performed with a standard sphygmomanometer using a cuff of appropriate size as recommended by the Working Group of the National High Blood Pressure Education Program [15]. Reference values and definitions of normal blood pressure were based on the Second Task Force Report [16].

VUR units were classified according to the International Reflux Study Committee [17]. For statistical analysis, VUR was classified as mild/moderate (grades I–III) and severe (grades IV–V). Renal damage classification was qualified according to the findings obtained with ^{99m} Tc-DMSA and defined as normal (no alterations), mild (localized damage), moderate (two or more scars), and severe (contracted unit). After 24 months patients were investigated by a conventional voiding cystourethrogram (VCUG) or by a direct isotope cystogram. The criterion for resolution of the reflux was its absence in a single exam. When reflux persisted, subsequent exams were performed at 3-year intervals.

Survival analyses were performed by the Kaplan-Meier method in order to evaluate reflux resolution. Differences between subgroups (mild vs moderate/severe reflux) were assessed by the two-sided log rank test. The chi-square test with Yates correction was used for the comparison of proportions. For patients with bilateral reflux, only the unit with the higher grade of reflux was considered for analysis. Relative risk (RR) and 95% confidence intervals (95% CI) were used for group comparison. The paired two-sample t -test was used for comparison of continuous variables (nutritional parameters at admission and at the end of follow-up).

Table 1 Distribution of reflux grades and renal damage (RD) according to gender (*NI* not investigated by DMSA scan, *VUR* vesicoureteral reflux)

Grade of VUR	Male			Female		Total
	RD (+)	RD (−)	NI	RD (+)	RD (−)	
I	0	2	0	0	2	4
II	1	6	0	0	3	10
III	2	12	1	2	5	22
IV	6	12	2	1	3	24
V	13	8	0	2	0	23
Total	22	40	3	5	13	83

The study was approved by the ethics committee of UFMG and informed consent was obtained from the parents or persons responsible.

Results

A total of 53 children were included in the analysis. Forty-one were males (77.4%) and 12 (22.6%) were females. There was a predominance of white patients (77.5%). The mean age at admission was 2 months (1–18 months). Seven infants were referred late, after 6 months of life, in spite of an antenatal diagnosis of pelvic dilatation. Four of them had urinary tract infection before admission. In the laboratory evaluation at admission, serum renal function was within the normal limits for the age. Serum urea ranged from 10–44 mg/dl (mean, 23.8 mg/dl, SD, 10) and serum creatinine ranged from 0.2–0.8 mg/dl (mean 0.46 mg/dl, SD, 0.16). The mean estimated glomerular filtration rate was 75 ml/min (range 28–172, SD, 28). The mean weight-for-age z-score was −0.32 (range −2.33 to +2.93, SD 1.1). Ten infants presented with a weight-for-age z-score of less than −1.29 (19%) and five presented a z-score of less than −1.89 (9.5%). The mean height-for-age z-score was −0.41 (range −4.43 to +1.93, SD 1.2). Eleven infants presented with a height-for-age z-score of less than −1.29 (20.8%) and seven with a z-score of less than −1.89 (13%).

Thirty (56.6%) presented bilateral VUR, for a total of 83 renal units. Six patients (11%) presented duplex systems. The distribution of reflux is presented in Table 1. Severe reflux (IV/V) was more frequent in males (68.3%) than in females (50%), but the difference was not significant (X^2=1.3, p =0.20).

On the first DMSA renal scan, renal damage was detected in 27 (33.7%) of the 80 units evaluated (Table 1). The distribution of severity of renal damage was as follows: normal, 53 units (66%); mild, 8 (10%), moderate, 9 (11%), and severe, 10 (13%). There was a significant correlation between severe reflux and the presence of renal damage. Of the 34 patients with severe reflux, 20 (58.8%) presented renal damage, whereas, only three (15.8%) of 19 units of patients with mild/moderate reflux presented scars (X^2=9.2, p =0.002). Fig. 1 illustrates the association between grade of reflux and renal damage. The prevalence of renal damage according to grade of

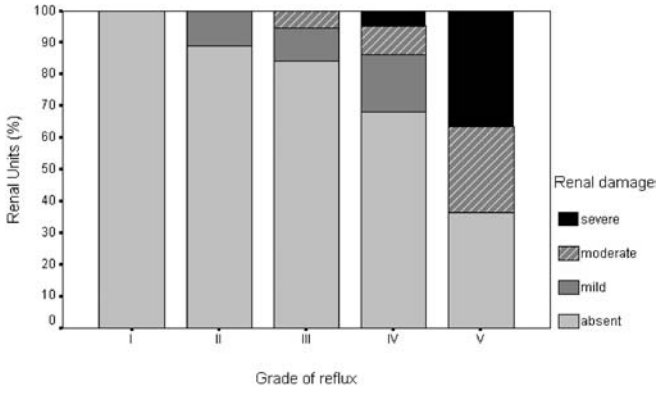

Fig. 1 Correlation between grade of reflux and severity of renal damage

VUR was: I (0%), II (11%), III (16%), IV (32%), and V (65%). There was a slightly higher prevalence of renal damage in males, although without significance. Damage occurred in 19 (46.3%) of 41 males and in four (33.3%) of 12 females (X^2=0.64, p =0.32). There was no difference in renal damage at entry between children referred before or after 6 months of age (X^2=0.05, p =0.54).

Clinical course

Mean follow-up time was 66 months (SD, 49, range 6–200 months) for 51 (96%) patients. A total of 39 (76%) patients were followed up for more than 2 years and 24 (47%) for more than 5 years. Two patients were lost to follow-up. Forty-seven patients (89%) were treated with continuous low-dose antibiotic prophylaxis. Six patients (11%) were submitted to surgical procedures: two with bilateral grade V VUR (neonatal diversions); two with unilateral grade V VUR with repeated UTI (ureteral reimplantation); one with a unilateral grade V contracted renal unit (nephrectomy); and one with duplex system, renal dysplasia and UTI (heminephrectomy). Urinary tract infection during follow-up occurred in 12 (25%) of 47 children conservatively managed and in three submitted to surgery. Seven patients presented one UTI episode, and four presented two episodes. There was no association between urinary tract infection and gender (X^2=0.07, p=0.67), grade of VUR (X^2=0.08, p=0.89), and presence of renal damage at admission (X^2=0.05, p=0.92). There was no difference in occurrence of UTI between children referred before or after 6 months of age (X^2=0.45, p=0.37).

At the end of follow-up, VUR resolution was evaluated in 40 patients (56 renal units) submitted to conservative management. Spontaneous resolution of VUR was observed in 15 (37.5%) patients and in 25 units (45%). Fig. 2 illustrates the survival analysis curve for spontaneous resolution of VUR. There was an association between VUR grade and time of resolution (log-rank, 5.6, p=0.017). At 48 months after diagnosis, 75% of cases of mild reflux (I–III) and 37% of severe reflux (IV–V) had resolved.

Forty-five renal units were evaluated for damage at the end of follow-up. Renal damage was detected in 14 (31%) of the 45 units evaluated. The distribution of severity of renal damage was as follows: normal, 31 units (69%), mild, 3 (6.6%), moderate, 3 (6.6%), and severe, 8 (18%). There was no occurrence of new scars in refluxing renal units.

In the laboratory evaluation at the end of the follow-up, serum renal function remained within the normal limits for age. Serum urea ranged from 17–45 mg/dl (mean, 26 mg/dl, SD, 7) and serum creatinine ranged from 0.2–1.2 mg/dl (mean 0.53 mg /dl, SD, 0.22). The mean estimated glomerular filtration rate was 128.5 ml/min (range 55–179, SD, 32). The upper limit of creatinine was observed in a 16-year-old male patient with bilateral severe reflux with an estimated glomerular filtration rate of 105 ml/min. This patient underwent temporary cutaneous ureterostomy and subsequently ureteral reimplantation during the first year of life. There was no UTI during follow-up. He developed systolic hypertension

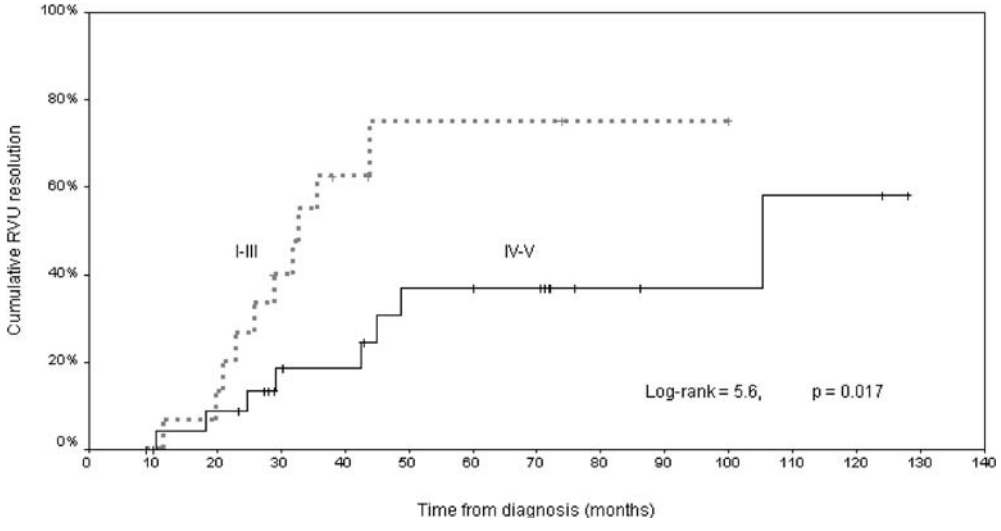

Fig. 2 Influence of grade on reflux resolution

(systolic blood pressure of 145 mmHg and diastolic pressure of 75 mmHg at the last visit to the outpatient clinic). The initial DMSA scan showed severe bilateral renal damage, and a follow-up DMSA showed the same pattern by the age of 12 years. Sonographic control demonstrated bilateral renal scars but with maximum renal longitudinal diameters within the normal limits for age.

There was an improvement of nutritional parameters evaluated in 50 children at the end of follow-up. The mean weight-for-age *z*-score was +0.19 (range −2.70 to +2.53, SD 1). The mean height-for-age *z*-score was +0.24 (range −2.81 to +2.50, SD 1.1). Only five children presented with weight-for-age and height-for-age *z*-scores of less than −1.29 (10%). There was a significant difference between mean weight-for-age *z*-score at admission and at the end of follow-up (t=−3.4, p=0.001). This difference was also observed for height-for-age *z*-score (t=−3.7, p=0.001).

Discussion

We reported a retrospective cohort study of infants with prenatally detected primary VUR. There was a preponderance of males (77.5%) and higher reflux grades (III–V, 83%). Overall, 34% of the units presented renal damage at admission. A number of series of prenatally detected VUR have been reported in the last 15 years [3, 4, 6,18, 19, 20, 21, 22]. Data from these series have shown that reflux identified by investigation of fetal hydronephrosis predominates in males with bilateral moderate to severe reflux. An important finding of these studies is that many infants presented renal damage at initial evaluation before UTI occurred [1]. In our series, of 80 refluxing renal units evaluated by DMSA scan, 27 (34%) presented damage. Severe renal damage (contracted renal unit) was observed in ten units (15%) with a higher grade of reflux (Fig. 1). Anderson and Rickwood [6] also demonstrated an association between reflux grade and presence and severity of renal damage. In the larger published series, Yeung et al. [3] showed a 33% prevalence (78/236 units) of renal abnormalities. Similarly, they found a strong association between severe reflux and renal damage. On the other hand, in contrast to our findings, Yeung et al.[3] detected a significantly higher prevalence of abnormal kidneys in male units. However, our smaller sample probably can explain the absence of significance in our series. Male infants with VUR grade V and severe renal damage have been considered to be a subgroup within primary VUR patients. In our series, 91% (21/23) of VUR grade V and 70% (7/10) with severe renal damage occurred in male renal units. This fact has become clearer after the advent of prenatal diagnosis of sterile neonatal reflux. Nevertheless, many previous studies of VUR detected in the investigation of UTI have already reported a preponderance of boys with severe reflux and generalized renal damage [23,24]. The generalized type of renal damage with small kidneys and smooth outline associated with severe reflux in male infants before UTI indicates a congenital maldevelopment origin. Histological studies have identified congenital renal diseases consisting of renal hypoplasia and renal dysplasia with primitive ducts in nephrectomy specimens from patients with unilateral VUR [25,26]. The etiology of this renal damage is unknown, although many hypotheses have been raised to explain these findings. Mackie and Stephens [27] proposed the "ureteric bud theory," in which VUR and associated renal dysplasia may represent separate expressions of a malformed urinary tract. Transient obstruction of the male urethra during embryological development is an attractive hypothesis to explain the predominance of boys with severe reflux and renal dysplasia [28, 29, 30]. Urodynamic findings of detrusor hypercontractility and increased bladder wall thickness in infants with gross reflux partially support this hypothesis [3,31]. However, these theories do not account for infants of both genders with gross reflux and normal kidneys. Taken together, these findings suggest that males with severe bilateral reflux and associated renal dysplasia possibly represent an extreme point in the spectrum of classic primary VUR. Some authors have hypothesized the role of mutations of unknown genes with incomplete penetrance and predominant expression in these infants [32]. An early recognition of this condition is essential to planning a rational and tailored management of these infants.

After a median follow-up time of 66 months, spontaneous resolution of conservatively managed VUR was observed in 25 (45%) of 56 units in our series. The outcome of prenatally detected VUR has been little studied. Farhat et al. [22] reported a resolution rate of 46% for 34 units (grades III–V) by age 20 months. Yeung et al. [3] reported that 70% of the cases of mild reflux and 43% of the cases of severe reflux resolved by 15 months of follow-up. A low resolution has been reported for grade V reflux, i.e., 0–30% during a follow-up of 2–5 years, whereas grade IV was often reported to have a resolution rate of more than 50% [33]. A lower resolution rate was estimated by survival analysis of our series. For example, it was estimated that only 20% of the cases of mild reflux and 14% of the cases of severe reflux would have disappeared by 24 months. However, this estimate can be influenced by sample size, follow-up time, and the frequency of VCUG after the diagnosis of VUR. Currently, there is a wide variation regarding the schedule of sequential VCUGs. Some authors recommend intervals of 6–18 months [34]. We have adopted a more conservative approach (a 2–3 year interval between VCUGs) due to several factors, including a concern about the possible consequences of repeated invasive procedures and the considerable costs of a more strict surveillance of the reflux [35, 36, 37]. Interestingly, in a recent elegant study, Thompson et al. [38] demonstrated that establishing a tailored schedule of VCUGs (every 2 years in children with mild reflux and every 3 years in children with moderate/severe VUR) yields a substantial reduction of average numbers of VCUGs and of costs, with a modest increase in antibiotics exposure.

In the medium-long-term follow-up of the present study, the clinical outcome of prenatally detected VUR was relatively benign. Renal function remained within normal limits for age in all patients and no new renal scars developed during follow-up. However, despite prophylactic antibiotics since the first day of life in most patients, 25% of children had breakthrough UTIs during follow-up. There was no difference in incidence of UTI between genders, reflux grades, or types of renal damage at admission. Our incidence of recurrent UTI was comparable to previously reported series. The proportion of children with such infections varies between 4% and 28% [3, 4, 6, 21]. Lama et al. [9] compared the features and outcome of primary VUR detected in neonates with antenatal hydronephrosis and in infants less than 1 year old affected by UTI. The recurrence of UTI was observed in 20% (7/34) of the prenatal group and in 46% (27/53) of the infants. Sjostrom et al. [39] reported a cohort of infants with severe reflux and showed that half of the children had breakthrough UTIs during follow-up. Interestingly, they found a strong correlation between recurrent infections, bladder dysfunction, and no reflux resolution. Thus, the investigation and management of bladder dysfunction may possibly contribute to a reduction of UTI recurrence and to an improvement of reflux. However, the assessment of dysfunctional elimination syndrome in this age group is troublesome, and noninvasive methods must be developed to permit early detection and correct treatment [40].

Few reports have examined the effect of VUR on physical growth in children. Our data showed a remarkable improvement in nutritional parameters at the end of follow-up. Polito et al. [41] have shown that patients with bilateral VUR and renal damage have significantly lower height than controls. We could not identify any variable associated with nutritional impairment at admission. Nevertheless, the small size of our sample possibly contributed to this absence of correlation. On the other hand, the same group has reported that none of the patients with prenatally detected VUR had a height *z*-score below –2, nor a weight-for-height index below 90% during follow-up [42]. Possibly, the characteristics of our population from a developing country could explain the prevalence of undernourished infants at admission. However, they do not satisfactorily account for the improvement in nutritional features. We may speculate that the strictly regular follow-up contributed in part to the favorable clinical evolution of our cohort.

This study has several limitations, including its retrospective observational design, the number of patients, the inconsistency of initial management for patients referred later, and the large variation in follow-up time. Some of these limitations are inherent to retrospective cohort studies, such as the amplitude of follow-up time and can be outweighed by adequate survival analysis. The size of our sample, for example, might have precluded the demonstration of the association between gender and renal damage as shown by others [3]. Nevertheless, all patients were submitted to a systematic protocol by the same medical team, and almost half the cohort was followed for more than 5 years. Our study corroborates data obtained in other infant reflux series that emphasized the heterogeneity of this disorder. Our results suggest that the clinical course of prenatally detected VUR followed up on a medium-long-term basis is relatively benign. However, there are groups of patients, predominantly males, with severe bilateral reflux and congenital kidney malformation who seem to represent an extreme spectrum of primary VUR and probably need a tailored approach to avoid progression of renal disease.

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