



ORIGINAL ARTICLE

Reflux nephropathy and scarring nephropathy: So close and yet so different[☆]



Víctor M. García Nieto^{a,*}, Margarita Monge Zamorano^b, Luis Antón Hernández^c,
 María Isabel Luis Yanes^a, Patricia Tejera Carreño^a, Teresa Moraleda Mesa^a

^a Sección de Nefrología Pediátrica, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

^b Servicio Canario de Salud, Centro de Salud de Tacoronte, Tacoronte, Santa Cruz de Tenerife, Spain

^c Servicio de Cirugía Pediátrica, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

Received 10 May 2021; accepted 2 August 2021

Available online 2 July 2022

KEYWORDS

Albuminuria;
 Kidney concentrating
 ability;
 N-
 acetylglucosaminidase;
 Reflux nephropathy;
 Vesicoureteral reflux

Abstract

Objectives: Reflux nephropathy is a radiologic condition commonly used to express the existence of renal morphological lesions in patients who have or had vesicoureteral reflux (VUR). This morphological concept is used based on the image data collected, without conducting basic complementary renal function studies. The present study was designed to demonstrate that patients with active VUR present different functional renal alterations from those shown by patients with disappeared VUR.

Methods: Longitudinal descriptive retrospective analysis including 89 children (46 M, 43 F) with VUR diagnosis through a standard voiding cystourethrogram (VCUG). The basic renal function tests collected were the maximum urinary osmolality (UOsm) and the urinary albumin/creatinine and NAG/creatinine ratios. The data collected corresponded to two moments, when VUR was diagnosed and when it had already disappeared.

Results: Quantitative differences were verified in the three functional parameters when comparing those corresponding to both moments of the study. In the qualitative analysis, in relation to the intensity of the VUR, differences were observed in UOsm at diagnosis and in the albumin/creatinine ratio once the VUR had cured. At this last moment, a significant increase in the albumin/creatinine ratio was observed in patients with loss of renal parenchyma in relation to those without residual morphological lesions.

Conclusions: Concentrating ability defect is the most frequent finding in children with active reflux (true reflux nephropathy), whereas the most frequent functional disturbance found, once VUR has cured, is an increase in urinary albumin excretion, related to parenchymal damage.

[☆] Please cite this article as: García Nieto VM, Monge Zamorano M, Antón Hernández L, Luis Yanes MI, Tejera Carreño P, Moraleda Mesa T. Nefropatía de reflujo y nefropatía cicatrizal. Dos entidades tan cercanas pero funcionalmente tan distintas. *An Pediatr (Barc)*. 2022;97:40–47.

* Corresponding author.

E-mail address: vgarcianieto@gmail.com (V.M. García Nieto).

The term dysplastic-scarring nephropathy, could be more appropriate for patients with residual morphological lesions and impaired renal function, once VUR is cured.

© 2021 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

PALABRAS CLAVE

Albuminuria;
Capacidad de
concentración renal;
N-
acetilglucosaminidasa;
Nefropatía de reflujo;
Reflujo vesicoureteral

Nefropatía de reflujo y nefropatía cicatrizal. Dos entidades tan cercanas pero funcionalmente tan distintas

Resumen

Objetivo: La nefropatía de reflujo es el término radiológico que se utilizó para expresar la existencia de lesiones morfológicas renales en pacientes con reflujo vesicoureteral (RVU). Este concepto morfológico se acuñó a partir de los datos de imagen recogidos aunque sin realizar estudios complementarios básicos de función renal. Este estudio se diseñó para demostrar que las pruebas de función renal básicas muestran resultados distintos en presencia de RVU activo y una vez desaparecido.

Pacientes y métodos: Estudio descriptivo retrospectivo longitudinal en el que se incluyeron 89 niños (46 V, 43 M) con RVU diagnosticado mediante cistouretrografía miccional seriada. Las pruebas básicas de función renal recogidas fueron la osmolalidad urinaria máxima (UOsm) y los cocientes urinarios albumina/creatinina y NAG/creatinina. Los datos acopiados correspondían a dos momentos, al diagnosticarse el RVU y cuando ya se había curado.

Resultados: Se comprobaron diferencias cuantitativas en los tres parámetros funcionales al comparar los correspondientes a ambos momentos del estudio. En el análisis cualitativo, en relación con la intensidad del RVU, se apreciaron diferencias en UOsm al diagnóstico y en el cociente albumina/creatinina una vez desaparecido el RVU. En este último momento, se observó un aumento significativo en el cociente albumina/creatinina en los pacientes con pérdida de parénquima renal en relación con aquellos sin lesiones morfológicas residuales.

Conclusiones: El defecto en la capacidad de concentración renal es el hallazgo más frecuente en niños con RVU activo (auténtica nefropatía de reflujo), mientras que una vez curado el RVU, la alteración funcional más frecuente es el aumento de la excreción de albúmina, en relación con el daño residual existente en el parénquima renal. Puesto que la alteración funcional es diferente en los niños con RVU activo y cuando ya no está presente, no se debería utilizar el mismo término para ambas situaciones puesto que, aunque próximas, son entidades distintas. El término nefropatía displásico-cicatrizal reflejaría mejor las características de estos pacientes una vez curado el RVU.

© 2021 Asociación Española de Pediatría. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Chronic pyelonephritis was the first term coined to describe permanent residual renal lesions observed in children with a history of one or more febrile urinary tract infections (UTIs).¹ In the 1960s, evidence emerged of a potential association between chronic pyelonephritis and vesicoureteral reflux (VUR), which motivated the diffusion of a new term, *reflux nephropathy*.² This new concept, initially based on radiological findings, referred to an association between VUR, renal scarring and the possibility of developing chronic renal disease,³ although little attention was given to the presence of other associated renal functional defects. In the late 1990s, avoiding this term was recommended, as it was established that sterile VUR did not cause scarring,⁴ and that infection of the renal parenchyma, rather than VUR, was the necessary condition for its development,⁵ which

means that VUR is not the actual cause of the scarring, but rather the acute inflammation of the renal parenchyma.^{4–7}

Thus, *acquired renal scarring* was proposed as an alternative to replace the term *reflux nephropathy*.⁸ However, the new term underemphasised congenital defects (dysplasia, hypodysplasia) that may be associated with VUR and that have come to be known as *congenital reflux nephropathy*.^{8,9}

Preliminary studies have shown that VUR interferes with renal tubule function. Thus, a reduction in renal concentrating ability^{10,11} and an increase in the urinary excretion of albumin¹² and of N-acetyl- β -glucosaminidase (NAG)¹³ have been reported.

We designed a study to assess whether the abnormalities observed in basic renal function tests were different when VUR was active versus, once VUR had resolved, only the residual congenital or acquired loss of renal parenchyma remained.

Sample and methods

Study design

We conducted a longitudinal retrospective and descriptive study including data corresponding to 89 patient aged less than 16 years (46 male, 43 female) with a diagnosis of VUR made by voiding cystourethrogram (VCUG) between January 2003 and December 2016. The patients had been followed up for a minimum of 2 years at the outpatient paediatric nephrology clinic of our hospital with at least the maximum urine osmolality (UOsm) documented in their health records by the end of the followup. Of these patients, 62 had undergone surgery and 27 had received conservative treatment.

The mean age at diagnosis was 23.9 months (standard deviation, 31.1; range, 0–164 months). Thirty-nine children received the diagnosis of VUR before age 6 months and 50 after. Seventy-one patients were evaluated for having more than 1 UTI. Another 16 underwent evaluation after detection of structural abnormalities in antenatal ultrasound examinations (hydronephrosis in 13 and small kidneys in 3). Macroscopic haematuria was the initial warning sign in the 2 remaining patients.

Vesicoureteral reflux was categorised into 5 grades (I–V) based on the classification of the International Reflux Study Committee.¹⁴ The highest grading was assigned to cases of bilateral VUR ($n=43$). Seventeen cases were classified as mild VUR (2 grade I, 15 grade II), 39 as moderate (grade III) and 33 as severe (27 grade IV, 6 grade V).

Vesicoureteral reflux was managed conservatively (with or without antibiotic prophylaxis) in 27 patients (30.3%), with open surgery in 15 cases (16.8%) and with endoscopic surgery in 47 (52.8%). Vesicoureteral reflux was resolved at a mean age of 5.86 years (SD, 3.65; range, 1.06–14.83). All patients were aged more than 2 years by the end of the followup (mean, 6.28 years; SD, 3.75; range, 2–16).

For the diagnosis timepoint, we used the data for samples obtained at the time closest to the VCUG. Samples for the determination of the renal function parameters under study were obtained at least 4 months after resolution of an acute pyelonephritis episode.

Inclusion criteria

The inclusion criteria were the following:

- Primary VUR diagnosed by VCUG that resolved with conservative or surgical management.
- Performance of at least 1 imaging test (ultrasound or a renal scan with ^{99m}Tc-dimercaptosuccinic acid [^{99m}Tc-DMSA]) at each of the 2 timepoints under study (at diagnosis and at the end of followup).
- Documentation in the health records of at least the la UOsm at the end of followup. We also collected data on other renal function parameters (albumin/creatinine and NAG/creatinine ratio) when available.

Exclusion criteria

We excluded all patients aged more than 16 years with VUR and all children of any age with a diagnosis of multicys-

tic renal dysplasia, pyeloureteral or vesicoureteral stenosis, posterior urethral valves or neurogenic bladder.

Assessment of renal structure

An ultrasound was performed at diagnosis in 85 patients and in every patient by the end of the followup ($n=89$). Mild hydronephrosis was diagnosed in children with an anteroposterior renal pelvis diameter of 0.5–2 cm, and moderate/severe hydronephrosis if the diameter was 2 cm or greater. A ^{99m}Tc-DMSA renal scan was performed in 72 patients at diagnosis and in 80 at the end of the followup. Congenital renal dysplasia was diagnosed based on detection of small-sized kidneys with structural abnormalities and a relative tracer uptake of less than 20% in the initial renal scan.¹⁵

Desmopressin challenge test

After voiding the bladder, the patient was given 20 µg of desmopressin intranasally, 0.2 mg (200 µg) of desmopressin in tablet form, or else 0.12 mg (120 µg) of oral lyophilisate (DDAVP MELT) that dissolves instantly in the oral cavity. After the administration of desmopressin, we collected 3 consecutive urine samples, at 90-minute intervals if the child had achieved bladder control. We imposed moderate restrictions on fluid intake. In the case of infants aged 1–12 months, we administered a 10 µg dose of desmopressin intranasally in the morning and restricted oral feeds to half the normal volume until 6 pm to decrease the risk of water intoxication. The maximum UOsm was recorded as the result of the challenge.^{11,16}

Laboratory tests

Urine creatinine was determined with a kinetic colorimetric assay based on the Jaffe method (Creatinine Jaffe Gen.2, Roche). Albumin was measured with a rate nephelometry method (array) and NAG activity using a colorimetry assay based on the hydrolysis of 3-cresolsulfonphthaleinyl-N-acetyl-β-D-glucosaminidase (Roche). The UOsm was measured with freezing point depression osmometer (Osmo Station OM-6050, Menarini Diagnostics).

Normal ranges

The normal ranges used as reference for the maximum UOsm following administration of desmopressin are available in a previous publication by our research group based on measurements in 125 healthy children.¹¹ In infants, the fifth percentile (P5) is 532 mOsm/kg for age 1–3 months, 616 mOsm/kg for age 3–6 months; 645 mOsm/kg for age 6–9 months and 740 mOsm/kg for age 9–12 months. In children aged more than 1 year, the lower limit of normal is 800 mOsm/kg.¹⁶ Normal ranges for age for the albumin/creatinine ratio and the NAG/creatinine ratio have also been published in the past.¹⁷

Table 1 Qualitative analysis of the renal function parameters in relation to the grade of VUR at the time of diagnosis and at the end of followup.

	Mild VUR		Moderate VUR		Severe VUR		P
Maximum UOsm at diagnosis (active VUR)	Normal 11	Decreased 3	Normal 22	Decreased 13	Normal 10	Decreased 20	.008
Maximum UOsm at end of followup (resolved VUR)	Normal 17	Decreased 0	Normal 37	Decreased 2	Normal 27	Decreased 6	ns
Albumin/creatinine at diagnosis (active VUR)	Normal 11	Elevated 1	Normal 25	Elevated 3	Normal 19	Elevated 8	ns
Albumin/creatinine at end of followup (resolved VUR)	Normal 16	Elevated 0	Normal 30	Elevated 3	Normal 23	Elevated 9	.02
NAG/creatinine at diagnosis (active VUR)	Normal 7	Elevated 0	Normal 13	Elevated 6	Normal 10	Elevated 4	ns
NAG/creatinine at end of followup (resolved VUR)	Normal 8	Elevated 0	Normal 22	Elevated 0	Normal 18	Elevated 0	–

NAG, N-acetyl- β -D-glucosaminidase; ns, not significant; UOsm, urinary osmolality; VUR, vesicoureteral reflux.

Statistical analysis

We used the Kolmogorov-Smirnov test to analyse the distribution of the data. In the descriptive analysis, we summarised categorical data as percentages and continuous data as mean \pm standard deviation if they were normally distributed, and otherwise (albumin/creatinine and NAG/creatinine ratios) as median and interquartile range (IQR). We compared variables with analysis of variance (ANOVA) or the Kruskal-Wallis test based on whether they were or not normally distributed. We assessed differences between paired samples by means of the Friedman test or Wilcoxon test. We used the chi square test to compare qualitative variable frequencies in groups, using the Yates correction as applicable. We calculated parameters of diagnostic performance to compare the data for cases of severe VUR to cases of mild/moderate VUR, both when VUR was active and when it was cured. Thus, we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), the positive likelihood ratio (LR+) and negative likelihood ratio (LR-) and the odds ratio (OR) with the corresponding 95% confidence interval (CI) for the 3 markers of renal function under study. The analysis was performed with the statistical software SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). We defined statistical significance as a *P*-value of less than .05.

Results

At the time of diagnosis, imaging findings were abnormal in 52 children: renal dysplasia ($n=14$), an area of unilateral scarring ($n=14$), several areas of scarring ($n=11$), mild isolated hydronephrosis ($n=7$), moderate-severe isolated hydronephrosis ($n=1$), duplicated collecting system ($n=4$) and renal agenesis ($n=1$). In addition, in 14 children, the acute-phase ^{99m}Tc -DMSA renal scan revealed areas of reduced tracer uptake characteristic of acute pyelonephritis. Renal imaging findings were normal in the rest of cases ($n=23$). Of the 14 children with renal dysplasia, 10 were male, 8 had grade IV VUR, and 6 had grade III VUR.

At the end of followup, 19 patients had unilateral renal scarring (one of them had a duplicated collecting system) 16 had several areas of scarring, 14 had a dysplastic kidney, as mentioned above, and 9 renal atrophy; one patient had renal agenesis. Renal morphology was normal in the 30 remaining children (3 with a duplicated collecting system). In short, 59 patients had a decrease in renal parenchyma of varying degree and 30 had an apparently intact renal parenchyma.

Table 1 presents the qualitative analysis of the renal function parameters in the patients, grouped by the grade of VUR a baseline, at diagnosis and at the end of followup. We found statistically significant differences in the UOsm, which at the time of diagnosis was decreased in 21% of children with mild VUR, 37% of children with moderate VUR and 67% of children with severe VUR. At the end of followup, we found a statistically significant difference in the frequency of patients with an elevated albumin/creatinine ratio based on the grade of reflux: none with mild VUR, 10% of children with moderate VUR and 39% of children with severe VUR (Table 1).

Using the data presented in Table 1, we analysed diagnostic performance parameters to compare the findings in severe VUR versus mild to moderate VUR in both timepoints under study (Table 2). The maximum UOsm had a sensitivity of 66.67% for discrimination of both types of VUR, which dropped to 18.18% after VUR resolved. The sensitivity of the other 2 parameters at the time of diagnosis was low. Once VUR had resolved, the specificity of both the maximum UOsm and the albumin/creatinine ratio was greater than 90%, and the specificity of the NAG/creatinine was 100%. The odds ratio was statistically significant for the maximum UOsm and urinary albumin at both timepoints (Table 2).

Table 3 presents the results of the quantitative and qualitative analysis of renal function parameters in the initial timepoint (at diagnosis of VUR) and at the end of followup (resolved VUR). We found significant differences in the quantitative values of the 3 parameters under study. At diagnosis, 46% of children exhibited a decreased concentrating ability, 18% an increased albumin/creatinine ratio, and 20% an increased NAG/creatinine ratio. At the end of followup, the renal concentrating ability (maximum UOsm) was decreased in only 9% of patients, and the albumin/creatinine ratio

Table 2 Results of the parameters used to analyse the diagnostic yield and accuracy of the basic renal function markers under study in severe versus mild to moderate vesicoureteral reflux at diagnosis and at the end of followup.

	Sen (95% CI)	Spe (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	Odds ratio P (95% CI)
Maximum UOsm at diagnosis (active VUR)	66.67% (47.19–82.71)	67.35% (52.46–80.05)	55.56% (43.73–66.78)	76.74% (65.74–85.02)	2.04 (1.27–3.28)	0.49 (0.29–0.85)	4.12 P = .004 (1.57–10.83)
Maximum UOsm at end of followup (resolved VUR)	18.18% (6.98–35.46)	96.43% (87.69–99.56)	75.00% (39.11–93.34)	66.67% (62.82–70.30)	5.09 (1.09–23.78)	0.85 (0.72–1.00)	6 P = .035 (1.13–31.7)
Albumin/creatinine at diagnosis (active VUR)	29.63% (13.75–50.18)	90.00% (76.34–97.21)	66.67% (40.05–85.69)	65.45% (59.23–71.19)	2.96 (0.99–8.87)	0.78 (0.60–1.02)	3.78 P = .048 (1.00–14.2)
Albumin/creatinine at end of followup (resolved VUR)	28.12% (13.75–46.75)	93.88% (83.13–98.72)	75.00% (46.76–91.11)	66.67% (61.42–71.53)	4.59 (1.34–15.69)	0.77 (0.61–0.96)	6 P = .01 (1.48–24.31)
NAG/creatinine at diagnosis (active VUR)	28.57% (8.39–58.1)	76.92% (56.35–91.03)	40.00% (18.38–66.38)	66.67% (57.46–74.76)	1.24 (0.42–3.67)	0.93 (0.63–1.27)	1.33 ns (0.30–5.83)
NAG/creatinine at end of followup (resolved VUR)	0% (0–18.53)	100% (88.43–100)	–	62.5% (62.5–62.5)	–	1 (1–1)	1.64 ns (0.03–86.68)

CI, confidence interval; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NAG, N-acetyl- β -D-glucosaminidase; NPV, negative predictive value; ns, not significant; PPV, positive predictive value; Sen, sensitivity; Spe, specificity; UOsm, urinary osmolality; VUR, vesicoureteral reflux.

Table 3 Quantitative and qualitative analysis of renal function parameters at the time of diagnosis of VUR and at the end of followup.

	Diagnosis of VUR (active VUR)		End of followup (resolved VUR)		P
Maximum UOsm (mOsm/kg) (n = 79)	670.1 ± 245.6		927.9 ± 119.3		< .001
Maximum UOsm Albumin/creatinine (µg/µmol) (n = 66)	Normal 43 (54%)	Decreased 36 (46%)	Normal 81 (91%)	Decreased 8 (9%) ^a	< .001
Albumin/creatinine NAG/creatinine (U/g) (n = 27)	1.93 (3.01)		1.05 (1.23)		< .001
Albumin/creatinine NAG/creatinine (U/g) (n = 27)	Normal 55 (82%)	Elevated 12 (18%)	Normal 69 (85%)	Elevated 12 (15%)	ns
NAG/creatinine	7.37 (14.98)		2.48 (1.8)		< .001
NAG/creatinine	Normal 39 (80%)	Elevated 10 (20%)	Normal 48 (100%)	Elevated 0 (-)	.003

NAG, N-acetyl-β-D-glucosaminidase; ns, not significant; UOsm, urinary osmolality; VUR, vesicoureteral reflux.

^a Several scars (n = 4), renal dysplasia or atrophy (n = 2), one scar (n = 1), apparently intact renal parenchyma (n = 1).

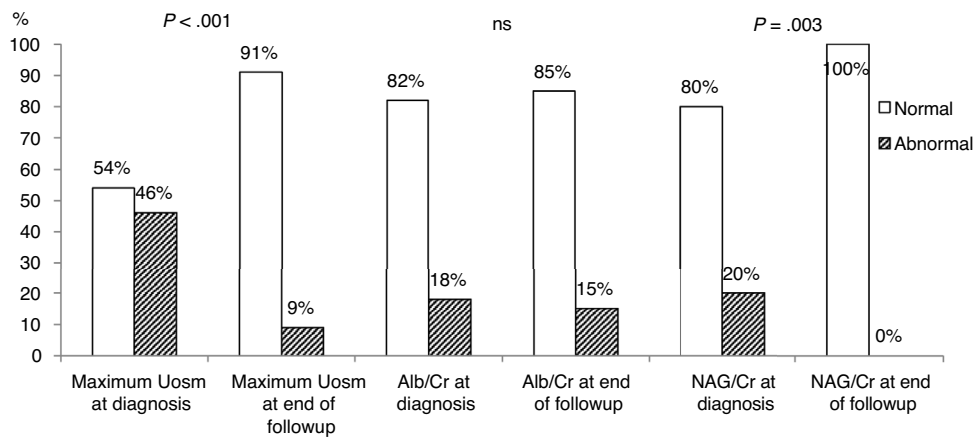


Figure 1 Bar chart representing the proportion of patients in the normal and abnormal range for the 3 analysed renal function parameters at the time of diagnosis of VUR and at the end of followup (data shown in Table 3).

Alb, albumin; Cr, creatinine; NAG, N-acetyl-β-D-glucosaminidase; ns, not significant; UOsm, urinary osmolality.

Table 4 Qualitative analysis of renal function parameters in relation to the loss of renal parenchyma at the end of followup (resolved VUR).

	No loss of renal parenchyma ^a		Loss of renal parenchyma ^b		P
Maximum UOsm	Normal 29	Decreased 1	Normal 52	Decreased 7	ns
Albumin/creatinine	Normal 26	Elevated 0	Normal 43	Elevated 12	< .001
NAG/creatinine	Normal 16	Elevated 0	Normal 32	Elevated 0	-

^a Mild VUR (n = 11), moderate VUR (n = 15), severe VUR (n = 4).

^b Mild VUR (n = 6), moderate VUR (n = 24), severe VUR (n = 29).

increased in 15%. The NAG/creatinine ratio was normal in every patient with resolved VUR (Fig. 1). Of the 8 patients with an impaired renal concentrating ability at the end of followup, 7 (87%) exhibited a decrease in renal parenchyma (Table 3).

At the end of followup, when we grouped patients based on whether or not they exhibited a decrease in renal parenchyma, the frequency of patients with an increased albumin/creatinine ratio was higher in the group with decreased renal parenchyma (Table 4).

We did not present the estimated glomerular filtration rate (eGFR) calculated with the updated Schwartz formula (2009) in any of the tables. Only 3 patients had an eGFR

of less than 90 mL/min/1.73 m² at the end of followup; two of them exhibited a decreased concentrating ability and an increased creatinine/albumin ratio.

Discussion

Many patients in the study were managed at a time when the approach to treatment was different from the current one. Children with VUR that had undergone renal function tests seemed to have the poorest outcomes. For this reason, the frequency of surgical management (endoscopic or open surgery) was higher compared to what is usually observed in hospitals in Spain, and the frequency of scarring at the end

of followup was higher compared to longitudinal studies on the subject, which reported an incidence of new scarring of approximately 10%.^{18,19}

As we mentioned in the introduction, *chronic pyelonephritis* was the first term used to describe residual lesions that appeared after one or more febrile UTIs.¹ Today, it may seem difficult to understand why renal lesions found in the forensic examination of children would contain bacteria by areas of fibrosis and nephron loss; features also observed in animal models of UTI, and this could be due to the lack of effective antibiotics in the beginning and the fact that the agents could not penetrate the scar tissue.²⁰ The persistent presence of bacteria suggests that a residual bacterial population could remain in the renal parenchyma and pelvis for a period of time after a febrile UTI and could cause recurrence in some patients.

As we already mentioned, the apparent association of chronic pyelonephritis and VUR was labelled *reflux nephropathy*.³ This is a radiological construct that translate to a decrease in renal parenchyma and that is confusing for several reasons. On one hand, renal development anomalies characterised by a decrease of renal parenchyma (dysplasia and hypoplasia) overlap with VUR; renal dysplasia is usually associated to massive VUR, most frequently unilateral and in male patients.^{8,9} Renal dysplasia is not caused by vesicoureteral reflux in isolation, but rather results from the association of 2 congenital anomalies of the kidney and urinary tract (CAKUT), which is relatively common in humans. In one of the best published editorials on the subject, Fernández Menéndez and Málaga Guerrero²¹ wrote that the term *reflux nephropathy* is misleading and that "this inadequate and confusing expression is still used today all too frequently. We will be able to completely eradicate its use once we stop being confused." On the other hand, as we noted in the introduction, the necessary condition for development of renal scarring after a febrile UTI is inflammation itself and not the presence of VUR.⁴ At the end of the 1950s, Shapiro et al.⁶ demonstrated in an experimental study in rats without VUR that induction of pyelonephritis in the animals produced an inflammatory response that eventually led to scarring.²⁰ In this sense, scarring is a loss of renal cortical parenchyma with secondary fibrosis resulting from the immune response to bacterial invasion, independently of the presence or absence of increased pressure in the urinary tract.²² Thus, it is well established that VUR is not the ultimate cause of scarring.^{4-7,20,23} However, a higher risk of renal scarring has been described in patients with VUR and urinary tract dilation.²⁴ Knowing that VUR is not a necessary condition for scar tissue formation, it is reasonable to explore why the severity of VUR may be associated with an increased risk of scarring. A possible explanation would be that pyelonephritis in patients with VUR and urinary tract dilation may be caused by bacteria that are more virulent for yet unknown reasons.^{25,26}

As concerns basic renal function tests, an experimental study in dogs published in the 1960s found a decreased renal concentrating ability after causing ureteral blockade.²⁷ Later, when desmopressin became available, researchers were able to measure the maximum UOsm, which turned out to decrease in patients, both paediatric and adult, with pyeloureteral obstruction.²⁸ Since then, a few studies have

described an association between VUR and a decreased renal concentrating ability.^{10,11,29}

In recent years, the renal mechanisms that explain the changes in water excretion in patients with increased pressure in the urinary tract have been investigated. Thus, studies have found decreased activity in sodium transporters in the tubules,³⁰ decreased expression of urea transporters³¹ and reduced aquaporin activity in the collecting duct.³⁰ Specifically, an experimental animal model of VUR found a decreased expression of aquaporins 1 and 2.³² All these functional changes promote the development of polyuria and salt wasting.

In this regard, in our sample a decreased concentrating ability was the most frequent functional impairment in patients with active VUR (Tables 1–3; Fig. 1), and it was more pronounced in patients with high-grade VUR (Table 2). Thus, a decreased maximum UOsm as the most frequent functional abnormality in patients with what we could call *true reflux nephropathy*. However, once VUR had resolved, the concentrating ability (maximum UOsm) improved (Table 2) and the number of children with impaired concentrating ability decreased from 46% to 9% (Table 3; Fig. 1). Of the 8 children with persistently decreased concentrating ability, 7 had some form of detectable renal parenchymal damage (Table 3).

There is evidence that supports that an increase in urinary albumin excretion is an early sign of glomerular damage in both diseases without nephron loss (diabetic nephropathy, obesity) and with a reduction in the number of nephrons, in addition to a good predictor of future cardiovascular disease. An increase in urinary albumin excretion has been described in patients with VUR,¹² but it is unclear whether this is due to the reduced renal parenchyma or to the increased pressure in the urinary tract.

In our case series, albuminuria was the most frequently observed abnormality in children with parenchymal loss once VUR had resolved (Table 3). Furthermore, patients that had more severe VUR at diagnosis had higher concentrations of albumin in urine at the end of followup (Tables 1 and 2) in association with the concomitant loss of renal parenchyma.

As for NAG, since the 1960s it is known that it originates from renal tissue,³³ as it is found in the lysosomes of proximal tubule cells; when these cells are damaged, it is released to the tubular lumen, resulting in its increased urinary excretion.³⁴ At first, it was used to assess the nephrotoxicity of aminoglycoside antibiotics, but NAG levels can also be elevated in patients with increased intratubular pressure, which is the case of urinary tract obstruction³⁵ and VUR.¹³ There is debate as to whether this increase in urinary NAG excretion is due to an increased pressure or to a decreased glomerular filtration rate.¹² In our sample, we found an increased urinary excretion of NAG in 20% of patients with active VUR that was probably secondary to increased pressure, as NAG levels normalised in all patients once VUR had resolved, which translates to a specificity of 100% (Tables 1–3, Fig. 1).

In short, from a functional standpoint, *reflux nephropathy* reflects a real process and applies when VUR is active, mainly translating into a decreased renal concentrating ability. On the other hand, albuminuria is the most frequent abnormality present in *acquired renal scarring* (once VUR has resolved), which is associated with the residual

parenchymal damage. Although these 2 renal diseases are closely related, they should not share a name because they cause different functional abnormalities in different morphological contexts, that is, when VUR is active and when it is cured. Lastly, we propose the term *dysplastic-scarring nephropathy* as a more fitting alternative to acquired renal scarring in patients with cured VUR, loss of renal parenchyma and impaired renal function.

In addition to its retrospective design, one of the limitations of this study was that morphological evaluations and/or renal function tests were not carried out in some of the patients at both timepoints.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

- Sommers SC, Gonick HC, Kalmanson GM, Guze LB. Pathogenesis of chronic pyelonephritis. II. Effect of repetitive infection. *Am J Pathol.* 1964;45:729–39.
- Hodson CJ, Edwards D. Chronic pyelonephritis and vesicoureteric reflux. *Clin Radiol.* 1960;11:219–31.
- Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. *Clin Nephrol.* 1973;1:132–41.
- Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. *Pediatr Nephrol.* 1997;11:108–20.
- Garin EH, Campos A, Homsy Y. Primary vesicoureteral reflux: review of current concepts. *Pediatr Nephrol.* 1998;12:249–56.
- Shapiro AP, Braude AI, Siemienski J. Hematogenous pyelonephritis in rats. IV. Relationship of bacterial species to the pathogenesis and sequelae of chronic pyelonephritis. *J Clin Invest.* 1959;38:1228–40.
- Winter AL, Hardy BE, Alton DJ, Arbus GS, Churchill BM. Acquired renal scars in children. *J Urol.* 1983;129:1190–4.
- Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. *J Urol.* 2010;184:265–73.
- Hiraoka M, Hori C, Tsukahara H, Kasuga K, Ishihara Y, Sudo M. Congenitally small kidneys with reflux as a common cause of nephropathy in boys. *Kidney Int.* 1997;52:811–6.
- Uehling DT. Effect of vesicoureteral reflux on concentrating ability. *J Urol.* 1971;106:947–50.
- García-Nieto V, García-Rodríguez VE, Luis-Yanes MI, Monge M, Arango-Sancho P, Garin EH. Renal tubular markers as screening tools for severe vesicoureteral reflux. *Eur J Pediatr.* 2019;178:525–31.
- Tomlinson PA, Smellie JM, Prescod N, Neil Dalton R, Chantler C. Differential excretion of urinary proteins in children with vesicoureteric reflux and reflux nephropathy. *Pediatr Nephrol.* 1994;8:21–5.
- Williams MA, Jones D, Noe HN. Urinary N-acetyl-beta-glucosaminidase as a screening technique for vesicoureteral reflux. *Urology.* 1994;43:528–30.
- International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteral reflux. *Pediatrics.* 1981;67:392–400.
- Mohanan N, Colhoun E, Puri P. Renal parenchymal damage in intermediate and high grade infantile vesicoureteral reflux. *J Urol.* 2008;180 4 Suppl:1635–8.
- Monnens L, Smulders Y, van Lier H, de Boo T. DDAVP test for assessment of renal concentrating capacity in infants and children. *Nephron.* 1981;29:151–4.
- García-Nieto VM, Afonso-Coderch M, García-Rodríguez VE, Monge-Zamorano M, Hernández-González MJ, Luis-Yanes MI. Diagnostic efficiency and quality indexes of several markers of renal function for detecting the loss of parenchyma in paediatric patients. *Nefrología.* 2012;32:486–93.
- Keren R, Shaikh N, Pohl H, Gravens-Mueller L, Ivanova A, Zautis L, et al. Risk factors for recurrent urinary tract infection and renal scarring. *Pediatrics.* 2015;136:e13–21.
- Mattoo TK, Chesney RW, Greenfield SP, Hoberman A, Keren R, Mathews R, et al. RIVUR Trial Investigators. Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. *Clin J Am Soc Nephrol.* 2016;11:54–61.
- Braude AI, Shapiro AP, Siemienski J. Hematogenous pyelonephritis in rats. III. Relationship of bacterial species to the pathogenesis of acute pyelonephritis. *J Bacteriol.* 1959;77:270–80.
- Fernández Menéndez JM, Málaga Guerrero S. ¿Es posible cambiar el paradigma flujo-céntrico? *Evid Pediatr.* 2006;2:17.
- Ragnarsdóttir B, Svanborg C. Susceptibility to acute pyelonephritis or asymptomatic bacteriuria: host-pathogen interaction in urinary tract infections. *Pediatr Nephrol.* 2012;27:2017–29.
- Garin EH. Primary vesicoureteral reflux; what have we learnt from the recently published randomized, controlled trials? *Pediatr Nephrol.* 2019;34:1513–9.
- Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics.* 2010;126:1084–91.
- de Man P, Cläesson I, Johanson IM, Jodal U, Svanborg Edén C. Bacterial attachment as a predictor of renal abnormalities in boys with urinary tract infection. *J Pediatr.* 1989;115:915–22.
- Hogan J, Mahjoub F, Larakeb AS, Vu Thien H, Hosany A, Bensman A, et al. *Escherichia coli* virulence patterns may help to predict vesicoureteral reflux in paediatric urinary tract infections. *Acta Paediatr.* 2015;104:e460–5.
- Selkurt EE. Effect of ureteral blockade on renal blood flow and urinary concentrating ability. *Am J Physiol.* 1963;205:286–92.
- Kekomäki M, Reunanen M, Vilkki P. Desaminocysteine-d-arginine vasopressin test in the evaluation and postoperative followup of obstructed kidneys in infancy and childhood. *J Urol.* 1982;128:981–3.
- Gobet R, Cisek LJ, Chang B, Barnewolt CE, Retik AB, Peters CA. Experimental fetal vesicoureteral reflux induces renal tubular and glomerular damage, and is associated with persistent bladder instability. *J Urol.* 1999;162:1090–5.
- Shi Y, Li C, Thomsen K, Jørgensen TM, Knepper MA, Nielsen S, et al. Neonatal ureteral obstruction alters expression of renal sodium transporters and aquaporin water channels. *Kidney Int.* 2004;66:203–15.
- Li C, Klein JD, Wang W, Knepper MA, Nielsen S, Sands JM, et al. Altered expression of urea transporters in response to ureteral obstruction. *Am J Physiol Renal Physiol.* 2004;286:F1154–62.
- Gobet R, Norregaard R, Cisek LJ, Peters CA, Nielsen S, Frøkiær J. Experimental congenital vesicoureteral reflux in sheep is associated with reduced renal expression levels of aquaporin 1 and 2. *J Urol.* 2008;179:2396–401.
- Walker PG, Woollen JW, Heyworth R. Studies on glucosaminidase. 5. Kidney N-acetyl-beta-glucosaminidase and N-acetyl-beta-galactosaminidase. *Biochem J.* 1961;79:288–94.
- Robinson D, Price RG, Dance N. Rat-urine glycosidases and kidney damage. *Biochem J.* 1967;102:533–8.
- Carr MC, Peters CA, Retik AB, Mandell J. Urinary levels of the renal tubular enzyme N-acetyl-beta-d-glucosaminidase in unilateral obstructive uropathy. *J Urol.* 1994;151:442–5.