Pop-off mechanisms as protective factors against chronic renal disease in children with posterior urethral valves

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ABSTRACT

Objective. To identify whether pop-off mechanisms act as protective factors against chronic or end-stage renal disease in patients with posterior urethral valves.

Materials and methods. A retrospective cohort study of patients with posterior urethral valves treated at a tertiary care children's hospital was carried out. Demographic, clinical, analytical, and radiological variables were collected. Considered as pop-off mechanisms were: unilateral high-grade vesicoureteral reflux with ipsilateral renal dysplasia and without involvement of the contralateral kidney, urinoma, prenatal urinary ascites, large bladder diverticulum, and persistent urachus. Multiple logistic regression and multivariate Cox regression were used for statistical analysis.

Results. 70 patients undergoing posterior urethral valve surgery in our institution from 2010 to August 2020 were included. 14 (20%) had pop-off mechanisms and 56 (80%) did not. Pop-off mechanisms protected against developing chronic renal disease (0% vs. 27%; p = 0.03) and could protect against the need for renal replacement therapy (0% vs. 9%; p = 0.58). Nadir creatinine values (mg/dl) were predictors for the development of chronic renal disease (0.37 vs. 0.53; p < 0.0001) and the need for renal replacement therapy (0.38 vs. 1.21; p < 0.001).

Conclusions. Pop-off mechanisms act as a protective factor against chronic renal disease in patients with posterior urethral valves. Nadir creatinine is a predictor of chronic renal disease and the need for renal replacement therapy. A larger sample size is needed to determine whether pop-off mechanisms protect against the need for renal replacement therapy.

KEY WORDS: CAKUT; Posterior urethral valves; Pop-off mechanisms; Chronic renal insufficiency.

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LOS FENÓMENOS *POP-OFF* COMO FACTORES PROTECTORES DE ENFERMEDAD RENAL CRÓNICA EN NIÑOS CON VÁLVULAS DE URETRA POSTERIOR

RESUMEN

Objetivos. Identificar si los fenómenos *pop-off* actúan como factores protectores de enfermedad renal crónica o terminal en pacientes con válvulas de uretra posterior.

Material y métodos. Estudio de cohortes retrospectivo de los pacientes con válvulas de uretra posterior tratados en un hospital infantil de tercer nivel. Se recogieron variables demográficas, clínicas, analíticas y radiológicas. Se consideraron fenómenos *pop-off*: reflujo vesicoureteral de alto grado unilateral con displasia renal ipsilateral y sin afectación del riñón contralateral, urinoma, ascitis urinaria prenatal, divertículo vesical grande y uraco persistente. Para el análisis estadístico se han utilizado regresiones logísticas múltiples y regresión de Cox multivariante.

Resultados. Se incluyeron 70 pacientes intervenidos de válvulas de uretra posterior y visitados en nuestro centro desde 2010 hasta agosto de 2020. Catorce (20%) presentaban fenómenos *pop-off* y 56 (80%) no. Los fenómenos *pop-off* fueron protectores para el desarrollo de enfermedad renal crónica (0 *vs.* 27%; p = 0,03) y podrían proteger de la necesidad de terapia renal sustitutiva (0 *vs.* 9%; p = 0,58). Los valores de creatinina nadir (mg/dl) fueron predictores de desarrollo de enfermedad renal crónica (0,37 *vs*. 0,53; p < 0,0001) y de necesidad de terapia renal sustitutiva (0,38 *vs*. 1,21; p < 0,001).

Conclusiones. Los fenómenos *pop-off* actúan como factor protector de enfermedad renal crónica en los pacientes con válvulas de uretra posterior. La creatinina nadir es un factor predictor de enfermedad renal crónica y de necesidad de terapia renal sustitutiva. Se necesita un tamaño de muestra mayor para determinar si los fenómenos *pop-off* protegen de la necesidad de terapia renal sustitutiva.

PALABRAS CLAVE: CAKUT; Válvulas de uretra posterior; Fenómenos *pop-off*; Insuficiencia renal crónica.

INTRODUCTION

Posterior urethral valves (PUV) are the most common cause of congenital lower urinary tract obstruction in children and lead to variable bladder outlet obstruction, causing significant impact on the upper urinary tract, renal

function, and in severe cases, also lung development. Up to 50% of patients have chronic renal disease (CRD) and the rate of end-stage renal failure in these patients is around 10-20%[1,2].

Several risk factors associated with poor renal function prognosis have been described. High nadir creatinine (lowest creatinine level during the first year of life, (greater than 1 mg/dl or 88.4 µmol/L) is considered an independent factor for end-stage renal failure[3], while patients with values between 35 and 75 µmol/L have a moderate risk of developing renal failure, and below 35 µmol/L the risk is considered low[4]. Gestational age at diagnosis, amniotic fluid volume, need for invasive ventilation in the neonatal period, and urinary diversion are also related to worse renal function[2,5].

On the other hand, pressure pop-off mechanisms have been described as protective factors of renal function due to their role in lowering intravesical pressure, but there is very little real scientific evidence of this benefit. Unilateral high-grade vesicoureteral reflux (VUR) with homolateral renal dysplasia, urinomas, urinary ascites, large bladder diverticula, and persistent urachus are considered pop-off mechanisms. Although these mechanisms have been historically defined as protective factors of renal function, most papers do not include these mechanisms as prognostic factors in patients with PUV, and study them separately or do not define them correctly[6-11]. Therefore, the results of the studies published to date are contradictory in terms of the supposed renal protection of pop-off mechanisms in patients with PUV.

Based on the hypothesis that pressure pop-off mechanisms act as protective factors for CRD in patients with PUV, the main objective of our study was to determine whether the presence of pressure pop-off mechanisms acts as a protective factor for CRD in this group of patients. Another objective was to determine whether they act as protective factors for end-stage renal disease and to analyze whether patient characteristics, comorbidities, or analytical parameters are predictors of chronic or end-stage renal disease in patients with PUV.

MATERIALS AND METHODS

A retrospective cohort study of patients with PUV treated at the Pediatric Surgery Outpatient Department of Sant Joan de Déu Hospital (Barcelona, Spain) from January 2010 to August 2020 was conducted. The primary outcome variable was the presence of CRD between stages 2-5 (defined as a glomerular filtration rate of less than 90 ml/min/1.73 m^2, according to the National Kidney Foundation's Kidney Disease Outcome Quality Initiative classification), and the secondary outcome variable was the presence of end-stage renal disease (defined as the need for renal replacement therapy [RRT], either peritoneal dialysis, hemodialysis, or renal transplantation). The prognostic variable (protective factor) was the presence of pressure pop-off mechanisms before PUV treatment, considering pop-off mechanisms as: unilateral high-grade VUR with ipsilateral renal dysplasia and no contralateral involvement, urinoma, prenatal urinary ascites, large bladder diverticulum, and persistent urachus.

Secondary variables were collected taking into account: age at PUV diagnosis, age at CRD diagnosis, age at end-stage renal disease diagnosis (measured at the time renal replacement therapy was indicated), need for urinary diversion and what type, type of replacement therapy (hemodialysis, peritoneal dialysis, renal transplantation), creatinine at diagnosis (mg/dl), nadir creatinine (lowest creatinine level during the first year of life, mg/dl), highest creatinine level during the first year of life (mg/dl), and radiological data (unilateral or bilateral VUR, unilateral or bilateral obstructive megaureter, multiple bladder diverticula).

All patients treated at our institution under 18 years old and having undergone a minimum follow-up period of one year from PUV treatment (at the latest, operated in August 2020) were included. Patients with loss of follow-up before one year after surgery and those with incomplete and/or irrecoverable data in terms of response or prognostic variable were excluded.

For statistical analysis, the Stata 14.2 software was used, and statistical significance was established at $p \leq 0.05$. Qualitative variables were described with percentages, and quantitative variables were described with mean and standard deviation or median and interquartile range, as applicable. A multiple logistic regression was planned to analyze the effect of pressure pop-off factors on the occurrence of CRD, including in the model any predictor variables that were statistically significant in a univariate analysis, and which, when removed from the final model, modified the Odds Ratio of the main prognostic variable (presence or absence of pressure pop-off mechanism) by more than 10%. The effect of the pressure pop-off factors was also analyzed with a study of survival free from renal failure by means of multivariate Cox regression, including in the final model any variables that, when removed, modified the Hazard Ratio of the main variable by more than 10%. A stepwise regression was performed to analyze the effect of each variable separately.

The study was approved by the Clinical Research and Ethics Committee of our institution (PIC-166-21).

RESULTS

70 patients who underwent surgery from January 2010 to August 2020 were included (Fig. 1).

Pop-off mechanisms were present in 14 patients (20%) vs. 56 patients (80%) with no pop-off mechanisms. There were 10 unilateral high-grade VUR cases, 4 diverticula, 2 ascites, 1 urinoma, and no persistent urachus. Of the 14

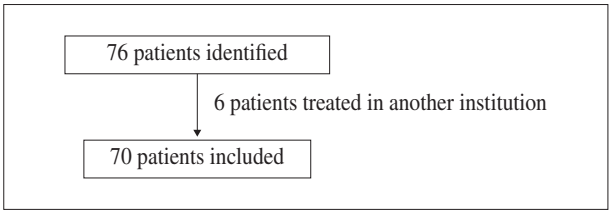

Figure 1. Flow diagram of study patients.

patients with pop-off mechanisms, 3 of them had more than one – 2 had VUR and an associated diverticulum, and 1 had VUR and urinoma.

Baseline patient characteristics are shown in table I. Of note is the higher rate of VUR in the group of patients with pop-off mechanisms, as well as the incidence of obstructive megaureter in the group without pop-off mechanisms. Also interesting is the absence of CRD development in the pop-off group, which means pop-offs could act as protective factors. The development of CRD was statistically significantly related to the absence of pop-off mechanisms (0% vs. 27%; p = 0.03).

Table II shows the risk factors for CRD. Nadir creatinine, highest creatinine in the first year of life, and highest urea in the first year of life were risk factors for development. On the other hand, the presence of pop-off mechanisms was a protective factor for CRD.

Multiple logistic regression was performed to identify risk factors for the development of CRD. Given the results found in the multiple logistic regression with such an extreme OR value for nadir creatinine, a stepwise regression was performed, including in the model any variables with a p-value <0.05, and excluding those with a p-value >0.1, in which all the variables were removed from the model and only nadir creatinine remained (Table III). Thus, we can affirm that for every mg/dl increase in the nadir creatinine value, the risk of developing CRD increases 15 times.

Table I. Baseline characteristics.

	Total (n = 70)	*Pop-off (n = 14)*	*No pop-off (n = 56)*	*p-value*
Age at treatment (years)	0.18	0.22	0.18	0.52
Median (IQR)	(0.03-0.58)	(0.02-0.51)	(0.04-0.82)	
Current age (years)	7.6	8.2	7.5	0.81
Median (IQR)	(5.5-10.9)	(4.2-10.2)	(5.5-11.2)	
Age at last follow-up (years)	7.4	7.6	7.4	0.93
Median (IQR)	(4.1-10.1)	(4.1-10.1)	(4.0-10.1)	
Creatinine at nadir (mg/dl)	0.39	0.37	0.4	0.17
Median (IQR)	(0.35-0.47)	(0.35-0.4)	(0.35-0.49)	
Urea at nadir (mg/dl)	19	19	19.5	0.88
Median (IQR)	(13-26)	(17-20)	(12.5-30.5)	
Vesicoureteral reflux				**0.039***
n (%)				
Yes	32 (46%)	10 (71%)	22 (39%)	
No	38 (54%)	4 (29%)	34 (61%)	
Multiple bladder diverticula				1.00
n (%)				
Yes	21 (30%)	4 (29%)	17 (30%)	
No	49 (70%)	10 (71%)	39 (70%)	
Obstructive megaureter				**0.016***
n (%)				
Yes	17 (24%)	0 (0%)	17 (30%)	
No	53 (76%)	14 (100%)	39 (70%)	
Chronic renal disease				**0.03***
(GFR < 90 ml/min/1.73 m^2)				
n (%)				
Yes	15 (21%)	0 (0%)	15 (27%)	
No	55 (79%)	14 (100%)	41 (73%)	
Renal replacement therapy				0.58
n (%)				
Yes	5 (7%)	0 (0%)	5 (9%)	
No	65 (92%)	14 (100%)	51 (91%)	

IQR: interquartile range; GFR: glomerular filtration rate.

Table II. Chronic renal disease risk factors.

	Total (n = 70)	*CRD (n = 15)*	*No CRD (n = 55)*	*p-value*
Age at treatment (years)	0.18	0.07	0.22	0.43
Median (IQR)	(0.03-0.58)	(0.04-0.46)	(0.02-0.89)	
Creatinine at nadir (mg/dl)	0.39	0.53	0.37	**<0.0001***
Median (IQR)	(0.35-0.47)	(0.46-0.71)	(0.34-0.4)	
Highest creatinine in the first year (mg/dl)	0.5	1.63	0.46	**<0.0001***
Median (IQR)	(0.42-0.76)	(0.74-2.43)	(0.41-0.63)	
Urea at nadir (mg/dl)	19	27	19	0.15
Median (IQR)	(13-26)	(12-56)	(13-23)	
Highest urea in the first year (mg/dl)	26.5	72.5	24	**0.0001***
Median (IQR)	(19.5-46.5)	(47.5-133)	(17.5-31)	
Vesicoureteral reflux				0.57
n (%)				
Yes	32 (46%)	8 (53%)	24 (44%)	
No	38 (54%)	7 (47%)	31 (56%)	
Pop-off				**0.03***
n (%)				
Yes	15 (20%)	0 (0%)	14 (25%)	
No	55 (80%)	15 (100%)	41 (75%)	
Multiple bladder diverticula				0.13
n (%)				
Yes	21 (30%)	7 (47%)	14 (25%)	
No	49 (70%)	8 (53%)	41 (75%)	
Obstructive megaureter				1.00
n (%)				
Yes	17 (24%)	3 (20%)	14 (25%)	
No	53 (76%)	12 (80%)	41 (75%)	

IQR: interquartile range; CRD: chronic renal disease.

Table III. Multiple logistic regression and stepwise regression of the risk of developing chronic renal disease.

	Univariate study			*Multivariate study*		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Age at surgery	4.02	0.37-43.2	0.25	Out of model		
Creatinine at nadir	8.6×10^{13}	$8165\text{-}9 \times 10^{23}$	**0.006***	14.9	5.13-24.7	**0.003***
Urea at nadir	0.87	0.75-1.001	0.052	Out of model		
Vesicoureteral reflux	0.37	0.03-3.9	0.41	Out of model		
Multiple bladder diverticula	10.3	0.8-132.1	0.07	Out of model		
Obstructive megaureter	0.54	0.04-7.9	0.66	Out of model		

OR: Odds Ratio; CI: confidence interval.

A CRD-free survival analysis was performed according to whether patients had pop-off mechanisms (Fig. 2). We observed that no patients with pop-off mechanisms developed CRD during follow-up.

Risk factors for RRT were also analyzed (Table IV). Risk factors for RRT were nadir creatinine, highest creatinine during the first year of life, nadir urea, and highest urea during the first year of life, in a statistically significant manner. A tendency for pop-off mechanisms to protect against the need for RRT was observed.

Finally, a survival analysis in terms of need for RRT was performed (Fig. 3). It revealed that none of the patients with pop-off mechanisms required RRT during follow-up.

DISCUSSION

The main morbidity in survivors with PUV is CRD, which develops in about 30% of patients before adolescence, progressing to end-stage renal failure in 10-20% of

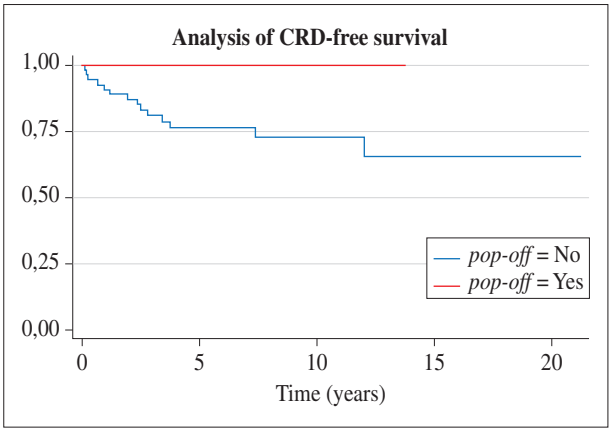

Figure 2. Survival analysis without chronic renal disease.

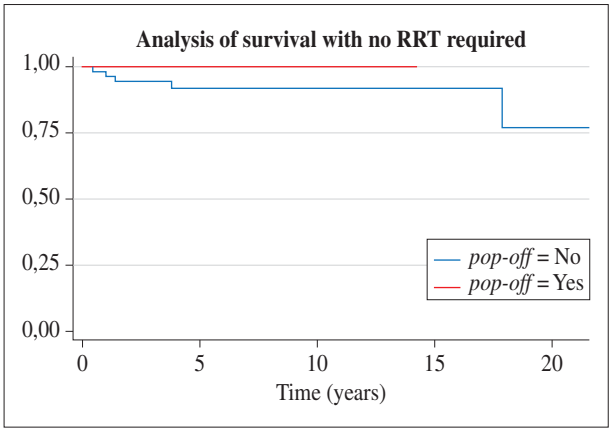

Figure 3. Analysis of survival with no renal replacement therapy required.

Table IV. Renal replacement therapy risk factors.

	Total (n = 70)	*RRT (n = 5)*	*No RRT (n = 65)*	*p-value*
Age at treatment (years)	0.18	0.08	0.19	0.80
Median (IQR)	(0.03-0.58)	(0.05-0.14)	(0.03-0.58)	
Creatinine at nadir (mg/dl)	0.39	1.21	0.38	**<0.001***
Median (IQR)	(0.35-0.47)	(0.71-2.17)	(0.34-0.46)	
Highest creatinine in the first year (mg/dl)	0.5	2.43	0.49	**0.002***
Median (IQR)	(0.42-0.76)	(2.08-3.66)	(0.42-0.72)	
Urea at nadir (mg/dl)	19	65	19	**0.002***
Median (IQR)	(13-26)	(58.5-107)	(13-23)	
Highest urea in the first year (mg/dl)	26.5	116	26	**0.003***
Median (IQR)	(19.5-46.5)	(71-160)	(18.5-36)	
Vesicoureteral reflux				0.65
n (%)				
Yes	32 (46%)	3 (60%)	29 (45%)	
No	38 (54%)	2 (40%)	36 (55%)	
Pop-off				0.58
n (%)				
Yes	15 (20%)	0 (0%)	14 (22%)	
No	55 (80%)	5 (100%)	51 (78%)	
Multiple bladder diverticula				0.63
n (%)				
Yes	21 (30%)	2 (40%)	19 (29%)	
No	49 (70%)	3 (60%)	46 (71%)	
Obstructive megaureter				1.00
n (%)				
Yes	17 (24%)	1 (20%)	16 (25%)	
No	53 (76%)	4 (80%)	49 (75%)	

RRT: renal replacement therapy; IQR: interquartile range.

cases[1,2,12-14]. Therefore, the ability to predict more accurately which type of patients are more likely to develop CRD would allow us to optimize follow-up and treatment of this group of patients.

Classically, pop-off mechanisms have been considered to be protective factors of renal function in patients with PUV, but the data is contradictory and most studies do not include them as prognostic factors, study them separately, or do not define them correctly[6-11,15-18]. Consequently, our study was specifically designed to try to clarify the real role that pop-off mechanisms play in the development of chronic or end-stage renal disease in patients with PUV.

In our study, 14 patients (20%) presented pop-off mechanisms, consistent with the rate reported in some studies[8,9,19]. However, the prevalence of pop-off mechanisms in another study was 65%, although they were not correctly defined, including clinical situations that are not considered to be true pop-off mechanisms[11].

As for VUR, the rate was higher in patients with pop-off mechanisms vs. those without (71% vs. 39%; p = 0.039). These results are consistent considering that one of the pop-off mechanisms is high-grade VUR with ipsilateral renal dysplasia without contralateral involvement, and that in our study, 10/14 (71%) patients had pop-off mechanisms. These results are consistent with the literature, in which high-grade reflux predominates in patients with PUV, and the left kidney is usually more affected[15,19,20]. However, we found no difference between the rate of VUR in patients who developed CRD and those who did not (53% vs. 44%, p = 0.57), as observed by Matsell et al.[6].

As for the rate of obstructive megaureter, the absence of obstructive megaureter in the group with pop-off mechanisms is noteworthy (0% vs. 30%, p = 0.016). This finding is probably explained by the reduction in bladder pressure caused by pop-offs, which act as an escape mechanism, so that the ureterovesical junction is not obstructed by excess intravesical pressure or detrusor hypertrophy. Furthermore, as in the case of VUR, this is probably also a selection bias, as many patients with pop-off mechanisms (71%) had VUR.

Pop-off mechanisms were statistically significantly protective against developing CRD (0% vs. 30%, p = 0.03). It also appears that they may have a protective role against the need for RRT (0% vs. 22%, p = 0.58). We did not find this last relationship to be statistically significant, as only 5 patients out of the 70 analyzed presented end-stage renal failure with the need for RRT. However, it is noteworthy that none of the 5 patients had pop-off mechanisms. Therefore, it is possible that, with more data and more patients with end-stage renal failure, this trend that pop-off mechanisms are protective against the need for RRT may be confirmed, since according to the data available, we currently do not have enough patients undergoing RRT to be able to perform a multiple logistic regression.

Nadir creatinine was the most important risk factor for developing CRD, such that for every mg/dl more, the risk of developing CRD increased 14.9 times (95%CI: 5.13-24.7; p = 0.003). This is consistent with the findings described in the literature[2,4,7]. We also observed that multiple bladder diverticula tended to be a risk factor for CRD, such that patients with multiple bladder diverticula had a 10.3-time (95% CI 0.8-132.1; p = 0.07) increased risk of developing CRD, although this association was not statistically significant. This result is probably explained by the fact that multiple bladder diverticula implies that it is a trabeculated bladder with poor accommodation, which secondarily affects the upper urinary tract and renal function.

Several analytical risk factors for RRT were identified: nadir creatinine (1.21 vs. 0.38; p < 0.001), highest creatinine in the first year (2.43 vs. 0.49; p = 0.002), nadir urea (65 vs. 19; p = 0.002), and highest urea in the first year (116 vs. 26; p = 0.003). Likewise, the "nadir creatinine" variable >0.69 perfectly predicts the need for RRT. That is, all patients with nadir creatinine levels >0.69 mg/dl ended up needing RRT, whereas none of the patients with nadir creatinine levels <0.69 mg/dl has required RRT so far. These findings are consistent with the literature[7,10]. However, it is interesting how all the studies include nadir creatinine levels as a predictor of chronic and end-stage renal failure, whereas, the role of urea, which could be another tool to identify the group of patients who will develop CRD, has not been analyzed.

Our study has the limitations inherent to the fact that it is a retrospective one – loss of information due to lack of registration in the clinical records, loss of patients during follow-up, or difficulty in retrieving external information from other institutions over the course of the study, among others. Likewise, the fact that none of the patients with pop-off mechanisms presented CRD prevented us from carrying out a multiple regression study including this variable. Finally, this is a preliminary study with a limited number of patients, as it only includes data from our institution. Nevertheless, it should be noted that this is a fairly large sample considering that it only includes patients from a single center. Data collection is currently underway in other Spanish settings to enlarge the sample, which will increase the internal and external validity of the study. Thus, this work forms the basis of a multicenter study whose results will certainly be of utmost relevance for the follow-up of patients with PUV.

In conclusion, this is the first study specifically conducted to analyze pop-off mechanisms that separates groups by considering all mechanisms together and defining them correctly (unlike many studies), without including clinical situations that are not considered true pop-off mechanisms (e.g., bilateral VUR). Furthermore, the sample size is large (70 patients), which demonstrates the role of pop-off mechanisms as a protective factor against developing CRD in patients with PUV.

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