Progression of Chronic Kidney Disease in Children With Vesicoureteral Reflux: The North American Pediatric Renal Trials Collaborative Studies Database

Thomas E. Novak,* Ranjiv Mathews, Karen Martz and Alicia Neu

From The Brady Urological Institute (TEN, RM) and Division of Pediatric Nephrology (AN), The Johns Hopkins Medical Institutions, Baltimore and EMMES Corp. (KM), Rockville, Maryland

Abbreviations and Acronyms

CKD = chronic kidney disease
eGFR = estimated GFR
ESRD = end stage renal disease
GFR = glomerular filtration rate
NAPRTCS = North American Pediatric Renal Trials and Collaborative Studies
SDS = standard deviation score
UTI = urinary tract infection
VUR = vesicoureteral reflux

* Correspondence: Pediatric Urology, The Johns Hopkins Hospital, Marburg 149, 600 North Wolfe St., Baltimore, Maryland 21287 (e-mail: Tnovak4@jhmi.edu).

Purpose: We describe a cohort of children with chronic kidney disease due to vesicoureteral reflux. We compared the rate of progression to end stage renal disease in those patients to the rate in children with another cause of chronic kidney disease and identified potential risk factors for progression.

Materials and Methods: We performed a retrospective cohort study using data from the North American Pediatric Renal Trials and Collaborative Studies Registry. Patients with vesicoureteral reflux as a cause of chronic kidney disease were compared to 2 other diagnostic cohorts. The 3 groups were compared with respect to baseline characteristics and progression to end stage renal disease based on diagnostic category. Multivariate analysis was performed to identify risk factors for progression to end stage renal disease using Cox proportional hazards regression model.

Results: Data on 6,981 patients were available for analysis. Patients with vesicoureteral reflux as a cause of chronic kidney disease had a significantly slower rate of progression to end stage renal disease than patients with renal aplasia, hypoplasia or dysplasia and all other causes (log rank $p < 0.0001$). On multivariate analysis of risk factors for progression to end stage renal disease in patients with vesicoureteral reflux as the cause of chronic kidney disease we found that, in addition to older age and more advanced chronic kidney disease stage, a history of urinary tract infection at registration was significantly associated with an increased risk of progression.

Conclusions: Children with vesicoureteral reflux had a slower rate of progression to end stage renal disease than children with another cause of chronic kidney disease even after controlling for multiple possible confounders. In children with vesicoureteral reflux as the cause of chronic kidney disease older age, higher chronic kidney disease stage and history of urinary tract infection are significantly associated with the risk of progression to end stage renal disease.

Key Words: kidney; kidney failure, chronic; risk; vesico-ureteral reflux; epidemiology

THE conventional approach to diagnosis and treatment in children with VUR is being reevaluated. Recent studies have questioned the impact of early diagnosis, antibiotic prophylaxis and recurrent UTIs on renal scarring in children with VUR.[1–3] However, it is well recognized that some children with VUR seem to have a poor renal outcome despite early and aggressive treatment for VUR. This encompasses a spectrum of CKD

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that in some cases culminates in ESRD requiring treatment with dialysis and/or kidney transplant. Regardless of etiology early recognition of CKD is of critical importance because it enables aggressive treatment for the ramifications of CKD and potentially for the beginning of therapy that may slow progression to ESRD. Identifying risk factors for progression could help delay the eventual need for renal replacement while identifying the most appropriate candidates for intervention.

The NAPRTCS Registry is a voluntary research effort comprising 140 pediatric kidney centers throughout North America that collects data on children with chronic kidney disease and those on dialysis, and status after kidney transplantation with the goal of improving the care delivered to those children. Using the NAPRTCS database we describe a cohort of children with CKD due to VUR. We compared the rate of progression to ESRD in those patients to the rate in children with another cause of CKD and identified potential risk factors for progression.

PATIENTS AND METHODS

We performed a retrospective cohort study using data from the NAPRTCS Registry, which has collected data on pediatric patients younger than 21 years with CKD since 1994. Eligibility for entry in the CKD database is an eGFR of 75 ml per minute per 1.73 m^2 or less, as calculated by the Schwartz formula.[4]

Patients with VUR as a cause of CKD were compared to 2 cohorts, including patients with congenital renal aplasia, hypoplasia or dysplasia and patients with CKD due to all other causes. The distribution of certain patient characteristics at the time of entry into the registry was compared among the 3 groups, including age, gender, race (white, black, Hispanic or other), CKD stage, registration year, eGFR, height and weight SDSs, history of UTI, history of urological surgery and history of prophylactic antibiotic use. CKD stage was defined by the National Kidney Foundation Kidney Disease Quality Outcomes Initiative Guidelines, including stage I—GFR 90 ml per minute per 1.73 m^2 or greater, stage II—GFR 60 to 89, stage III—GFR 30 to 59, stage IV—GFR 15 to 29 and stage V—GFR 15 or less.[5] Height and weight SDSs were calculated using American age and gender norms.[6] The chi-square test was used to compare categorical variables and the Kruskal-Wallis test was used for continuous variables.

Progression to ESRD was defined as termination from the CKD database due to kidney transplantation or the initiation of dialysis. The 3 groups were compared with respect to progression based on diagnostic category. Multivariate analysis was performed to identify risk factors for progression to ESRD using a Cox proportional hazards regression model. Covariates included in the model were CKD cause (VUR, renal aplasia or all other), age, CKD stage and height SDS at the time of registration, gender, race and year of registration. We then sought to identify risk factors for progression to ESRD in patients with VUR as a cause of CKD, again using a Cox proportional hazards regression model. Covariates of the final multivariate model were selected based on the results of backwards stepwise selection with all covariates remaining in the model demonstrating a significant effect at $p < 0.05$. Covariates considered for inclusion in analysis were age, CKD stage, height SDS, urological surgery history, UTI history and prophylactic antibiotic use at the time of registration, race, gender and year of registration. Data analysis was done using SAS® 8.2 with $p < 0.05$ considered significant.

RESULTS

Registration Characteristics

At the time of analysis data on 6,981 patients were available in the CKD Registry, including 590 (8.5%) with VUR as a cause of CKD, 1,212 with renal aplasia, hypoplasia or dysplasia (17.4%) and 5,179 with all other diagnoses (74.2%). Table 1 lists patient and demographic characteristics in the 3 patient cohorts at the time of entry into the registry. The distribution of patients in each of the 3 cohorts by year of registration and CKD stage at presentation was not statistically significant.

Progression to ESRD

The figure demonstrates that patients with VUR as a cause of CDK had a significantly slower rate of progression to ESRD than patients with renal apla-

Table 1. *Patient characteristics at registration*

	No. Primary Diagnosis (%)*		
	Reflux Nephropathy	Renal Dysplasia	All Other
Overall	590 (100.0)	1,212 (100.0)	5,179 (100.0)
Age (yrs):†			
0–1	74 (12.5)	465 (38.4)	877 (16.9)
2–5	90 (15.3)	233 (19.2)	778 (15.0)
6–12	234 (39.7)	322 (26.6)	1,678 (32.4)
13–17	192 (32.5)	192 (15.8)	1,845 (35.6)
18+	74 (12.5)	465 (38.4)	877 (16.9)
Male†	312 (52.9)	756 (62.4)	3,403 (65.7)
Race:†			
White	434 (73.6)	749 (61.8)	3,064 (59.2)
Black	35 (5.9)	206 (17.0)	1,058 (20.4)
Hispanic	79 (13.4)	181 (14.9)	700 (13.5)
Other	42 (7.1)	76 (6.3)	347 (6.7)
CKD stage:			
2	126 (21.4)	108 (8.9)	927 (17.9)
3	280 (47.5)	457 (37.7)	2,368 (45.7)
4	138 (23.4)	372 (30.7)	1,318 (25.4)
5	42 (7.1)	263 (21.7)	515 (9.9)
History:†			
Prophylactic antibiotics	301 (51.0)	303 (25.0)	1,301 (25.1)
UTI	368 (62.4)	264 (21.8)	1,487 (28.7)
Urological surgery	323 (54.7)	246 (20.3)	1,617 (31.2)

* Percents may not total 100% because of missing values.
† $p < 0.0001$.