Kidney Disease Progression in Autosomal Recessive Polycystic Kidney Disease

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Objective To define glomerular filtration rate (GFR) decline, hypertension (HTN), and proteinuria in subjects with autosomal recessive polycystic kidney disease (ARPKD) and compare with 2 congenital kidney disease control groups in the Chronic Kidney Disease in Children cohort.

Study design GFR decline (iohexol clearance), rates of HTN (ambulatory/casual blood pressures), antihypertensive medication usage, left ventricular hypertrophy, and proteinuria were analyzed in subjects with ARPKD (n = 22) and 2 control groups: aplastic/hypoplastic/dysplastic disorders (n = 44) and obstructive uropathies (n = 44). Differences between study groups were examined with the Wilcoxon rank sum test.

Results Annualized GFR change in subjects with ARPKD was −1.4 mL/min/1.73 m^2 (−6%), with greater decline in subjects age ≥10 years (−11.5%). However, overall rates of GFR decline did not differ significantly in subjects with ARPKD vs controls. There were no significant differences in rates of HTN or left ventricular hypertrophy, but subjects with ARPKD had a greater percent on ≥3 blood pressure medications (32% vs 0%, $P < .0001$), more angiotensin-converting enzyme inhibitor use (82% vs 27% vs 36%, $P < .0005$), and less proteinuria (urine protein: creatinine = 0.1 vs 0.6, $P < .005$).

Conclusions This study reports rates of GFR decline, HTN, and proteinuria in a small but well-phenotyped ARPKD cohort. The relatively slow rate of GFR decline in subjects with ARPKD and absence of significant proteinuria suggest that these standard clinical measures may have limited utility in assessing therapeutic interventions and highlight the need for other ARPKD kidney disease progression biomarkers. *(J Pediatr 2016;171:196-201)*.

Autosomal recessive polycystic kidney disease (ARPKD) affects approximately 1 in 20 000 children and is genetically and clinically distinct from the more common autosomal dominant form (autosomal dominant polycystic kidney disease).[1] ARPKD previously was considered a uniformly fatal disease in affected newborns, but with modern neonatal care, overall mortality has improved significantly. More than 70% survive beyond the newborn period, and >80% of those survive beyond 10 years of age.[2] ARPKD still carries significant morbidity, with more than 40% of patients progressing to end-stage renal disease by 15 years of age.[2] The phenotype of ARPKD, however, is quite variable: some patients progress to end-stage renal disease in infancy, whereas others may not require renal replacement therapy until later childhood and adolescence.[3] A smaller subset present primarily with liver manifestations, typically in adolescence and young adulthood.[4]

Despite the significant mortality and morbidity in this population, prospectively collected data on ARPKD progression are very limited. Most studies have relied on retrospective analyses and/or registries, which have inherent limitations.[3-5] One prospective study reported measured glomerular filtration rates (GFRs) obtained by 24-hour creatinine clearance measurements but did not report rates of GFR decline over time.[6] Factors that may contribute to the progression of kidney disease, specifically hypertension (HTN) and proteinuria, also have not been well characterized.

The need for these progression data is highlighted by the emergence of novel therapies that may slow the progression of disease. Although there are currently no disease-specific therapies that have been applied in patients with ARPKD, a number of therapies have shown promise in ARPKD animal models.[7,8] Unfortunately,

A/H/D	Aplastic/hypoplastic/dysplastic disorder	eGFR	Estimated glomerular filtration rate
ACEI	Angiotensin-converting enzyme inhibitor	GFR	Glomerular filtration rate
ARPKD	Autosomal recessive polycystic kidney disease	HTN	Hypertension
CKD	Chronic kidney disease	iGFR	GFR with the use of iohexol clearance
CKiD	Chronic Kidney Disease in Children	LVH	Left ventricular hypertrophy
CT	Collecting tubule	OU	Obstructive uropathy
		UPC	Urine protein to creatinine ratio

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the development of treatment trials in patients with ARPKD is hampered by the paucity of prospective data on GFR decline. In addition, surrogate markers for the progression of kidney disease, especially magnetic resonance imaging measurements of kidney volume used to quantitate the progression of kidney disease in ADPKD,[9] are not valid in ARPKD, because kidney size does not increase with progressive disease.[10]

The objective of this study was to describe the rates of GFR decline, HTN, and proteinuria in subjects with ARPKD currently enrolled in the prospective Chronic Kidney Disease in Children (CKiD) study. We also compared findings in the subjects with ARPKD with those of 2 control groups with other congenital renal diseases also enrolled in CKiD to better identify ARPKD-specific features of kidney disease progression that might differ from those of other congenital renal diseases.

Methods

Subjects with ARPKD and controls were selected from among those enrolled in CKiD, a longitudinal, prospective study of children with mild-moderate chronic kidney disease (CKD). Data in this manuscript were collected by CKiD Study with clinical coordinating centers at Children's Mercy Hospital and the University of Missouri - Kansas City and Children's Hospital of Philadelphia, Central Biochemistry Laboratory at the University of Rochester Medical Center, and data coordinating center at the Johns Hopkins Bloomberg School of Public Health. More than 50 pediatric nephrology sites in the US and Canada have participated and/or continue to participate in the study. The inclusion and exclusion criteria for participation in the study have been reported in detail elsewhere[11] (ClinicalTrials.gov: NCT00327860). Specific entry criteria relevant to this study include age 1-16 years, estimated GFR (eGFR) of 30-90 mL/min/1.73 m^2, absence of previous solid-organ or hematopoietic stem cell transplant and absence of severe syndromic disease. Subjects enrolled in CKiD undergo baseline evaluations, then yearly follow-up visits. The current study included all subjects with ARPKD currently enrolled in CKiD. Matched controls were obtained from 2 diagnostic groups with other congenital renal diseases: (1) aplastic/hypoplastic/dysplastic disorders (A/H/Ds); and (2) obstructive uropathies (OUs). These groups were chosen because they were likely to have a similar age distribution as the subjects with ARPKD and also are primarily tubulointerstitial diseases. Matching was performed to distinguish ARPKD-specific clinical features from those related to early-onset CKD in general.

Participants enrolled in CKiD undergo yearly determination of eGFR by the updated biomarker-based Schwartz GFR estimating formula, eGFR (ml/min per 1.73 m^2) = $39.8[\text{ht(m)}/\text{Scr(mg/dl)}]^{0.456}$ $[1.8/\text{cystatin C (mg/l)}]^{0.418}$ $[30/\text{BUN(mg/dl)}]^{0.079}$ $[1.076^{\text{male}}]$ $[\text{ht(m)}/1.4]^{0.179}$, and every-other-year measurements of GFR with the use of iohexol clearance (iGFR).[12] This eGFR formula has show strong correlation with corresponding iGFR measurements (R = 0.92).[12] An analysis of subjects with ARPKD confirmed a similar strong correlation between eGFR and iGFR (R = 0.96, data not shown).

Only subjects with at least 2 GFR measurements, whether iohexol-measured or estimated, were included. Subjects with ARPKD were matched 1:2 with A/D/H or OU controls for baseline GFR, age at study entry, and age at diagnosis. The primary outcome examined in this study was rate of GFR decline, reported both as percent (%) decline and absolute decline (expressed as GFR change in mL/min/1.73 m^2/y). Both iGFR and eGFR were used in progression calculations, with preference given to iGFR where available.[13] Blood pressure control and rates of left ventricular hypertrophy (LVH) and proteinuria also were investigated as secondary outcomes.

Casual blood pressures were obtained by standardized auscultatory methods at yearly visits. Ambulatory blood pressure monitoring was performed every 2 years by use of the SpaceLabs 90217 oscillometric device (SpaceLabs Healthcare, Issaquah, Washington). Echocardiography also was performed every 2 years to assess for the presence of LVH, defined as left ventricular mass ≥95th percentile (indexed to $Ht^{2.7}$ for age and sex). Methods for obtaining casual blood pressures, ambulatory blood pressure monitoring, and echocardiograms have been described elsewhere.[14,15] A subject was considered to have casual HTN if the baseline blood pressure at the first visit was ≥95th percentile for age/sex/height percentile.[16] Ambulatory HTN was defined as mean wake or sleep systolic blood pressure or diastolic blood pressure ≥95th percentile or wake or sleep systolic blood pressure or diastolic blood pressure load ≥25% according to published data.[17] Proteinuria was defined as a urine protein to creatinine ratio (UPC) of ≥0.2 mg/mg from first morning specimens obtained at yearly visits.

Statistical Analyses

Demographic and clinical characteristics were reported as median (IQR) or number, n (percent, %) for each group and compared descriptively between groups. Annualized percent and absolute change in GFR were calculated with the use of individual regressions (loglinear and linear, respectively) for each subject incorporating all available follow-up measurements. Differences (ARPKD vs each control group) were tested by the Wilcoxon rank-sum test or Fisher exact test. Matched differences were calculated as the difference between the value of a subject with ARPKD and the average value of the 2 matched controls, and these distributions were tested for difference from zero by Wilcoxon signed rank test. As a subanalysis, we stratified subjects with ARPKD and control groups by baseline GFR (≥45 and <45 mL/min/1.73 m^2) or age at study entry (≥10 and <10 years). All analyses were performed in SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

The baseline demographic and clinical features of the subjects with ARPKD and 2 control groups are shown in **Table I**. Subjects with ARPKD and controls were matched successfully on the selected factors; specifically, baseline GFR, age at study entry, and age at diagnosis were not significantly different between the subjects with ARPKD