Neurocognition in Children with Autosomal Recessive Polycystic Kidney Disease in the CKiD Cohort Study

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Abstract

Background—Autosomal recessive polycystic kidney disease (ARPKD) is an inherited disorder characterized by enlarged, cystic kidneys with progressive chronic kidney disease (CKD), systemic hypertension, and congenital hepatic fibrosis. Children with ARPKD can have early onset CKD and severe hypertension, both of which are known to have adverse neurocognitive effects. Objectives of this study were to (1) determine whether ARPKD patients have greater neurocognitive deficits compared to that of children with other causes of CKD, and (2) examine the relative prevalence of hypertension in ARPKD, a known risk factor for neurocognitive dysfunction.

Methods—We performed a cross-sectional, control-matched analysis of 22 ARPKD patients with mild-to-moderate CKD in the Chronic Kidney Disease in Children (CKiD) cohort study,

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compared with a control group of 44 children with other causes of CKD, matched based on glomerular filtration rate, age at study entry, and age at diagnosis.

Results—Children with ARPKD in this cohort had neurocognitive functioning comparable to children with other causes of CKD in domains of intellectual functioning, academic achievement, attention regulation, executive functioning, and behavior. Blood pressure parameters were similar between the two groups; however, ARPKD patients required a significantly greater number of antihypertensive medications to achieve similar BP levels.

Conclusions—ARPKD patients are potentially at risk for neurocognitive dysfunction due to early onset CKD and more severe hypertension. However, this study of children with mild-to-moderate CKD in the CKiD cohort did not demonstrate increased risk in children with ARPKD compared to children with other causes of CKD. Further studies are needed to determine if these findings are applicable to children with more severe manifestations of ARPKD.

Keywords

Autosomal recessive polycystic kidney disease; behavior; chronic kidney disease; hypertension; neurocognition; neuropsychological

Introduction

Autosomal recessive polycystic kidney disease (ARPKD, OMIM 263200) is an important genetic cause of progressive chronic kidney disease (CKD), and occurs in an estimated 1 in 20,000 live births [1]. Its characteristic clinical manifestations include kidney cysts derived from dilated collecting ducts, and ductal plate malformation in the liver, leading to dilation of biliary ducts, hepatic fibrosis, and portal hypertension. Clinical expression of the disease is widely variable. A subset of ARPKD patients has severe disease presenting in the perinatal period, with enlarged echogenic kidneys, oligohydramnios and pulmonary insufficiency. Others present later in childhood and have a more insidious course. The principal causes of morbidity and mortality in these children are progressive CKD, systemic hypertension, and hepatic fibrosis with resulting portal hypertension [2–7].

In recent years, there has been increasing recognition of behavioral and neurocognitive difficulties in children with CKD [8–11], as well as in children with both primary [12–15] and CKD-associated [16] hypertension. Children with ARPKD may therefore be at particular risk for adverse neurocognitive outcomes. Many children with ARPKD have renal dysfunction at or soon after birth, and are thus affected by CKD during the critical early years of neurodevelopment. In addition, many children with ARPKD have early onset and often severe hypertension [2, 3, 6, 17]; consequently, these children would carry the additional risk of neurocognitive problems associated with hypertension.

Despite these risk factors, there have been no prior studies specifically examining neurocognition in children with ARPKD. The current study sought to address this gap in knowledge by evaluating neurocognitive outcomes in children with ARPKD in the Chronic Kidney Disease in Children (CKiD) cohort study [18]. CKiD is a prospective, multicenter, longitudinal investigation of children with mild-to-moderate CKD due to a wide range of diagnoses, including ARPKD. Children in the CKiD study undergo comprehensive

neurocognitive assessments that include measures of intellectual functioning, academic achievement, attention regulation, executive functioning, and behavior.

In this study, we sought to examine whether there are disease-specific effects of ARPKD on neurocognitive outcomes. We sought to test the hypothesis that children with ARPKD will have a greater degree of neurocognitive dysfunction than children with other causes of early-onset CKD. Given findings in prior studies of children with CKD and hypertension [8, 10, 14, 19], we hypothesized that measures of executive functioning and attention regulation would be particularly affected in ARPKD. We also sought to examine the relative prevalence of hypertension, a known clinical risk factor for adverse neurocognitive outcomes.

Materials and Methods

Study Participants

Eligibility criteria for the CKiD cohort include age 1 to 16 years and estimated glomerular filtration rate (eGFR) between 30 and 90 mL/min|1.73m^2 calculated using the original Schwartz formula [20, 21]. Exclusion criteria include: renal, other solid organ, bone marrow or stem cell transplantation; dialysis treatment within the past three months; HIV or cancer diagnosis/treatment within the past twelve months; structural heart disease; current pregnancy or pregnancy within the past twelve months; genetic syndromes involving the central nervous system; history of severe to profound intellectual disability (i.e., intelligence quotient [IQ] < 40); and lack of fluency in English or Spanish [18]. The CKiD study protocol was approved by the Institutional Review Boards at all participating sites, and informed consent was obtained from all caregivers.

The current study was performed as a control-matched analysis within the CKiD cohort. All children enrolled in CKiD with a primary diagnosis of ARPKD who had completed their initial study visit were used as subjects for this analysis. Controls were defined as children enrolled in CKiD with a primary diagnosis of aplastic/hypoplastic/dysplastic kidneys; this diagnosis was selected as the control group since those patients would likely have a similar age distribution compared to children with ARPKD, and do not have a condition requiring potentially confounding treatment such as immunosuppression. Controls were matched with ARPKD subjects in a 2:1 ratio, based on baseline ieGFR (GFR measured by plasma disappearance of iohexol [iGFR], or eGFR if iGFR not available), age at study entry, and age at diagnosis. A second control group with aplastic/hypoplastic/dysplastic kidneys was also analyzed; the second control group was matched with ARPKD subjects based on prevalence of low birth weight and seizures, in addition to the other factors.

Neurocognitive Testing

Comprehensive age-specific neurocognitive assessments are performed in CKiD study participants six months after study entry, and again every two years after entry. These include measures of intellectual functioning (Wechsler Abbreviated Scales of Intelligence [WASI] [22], Wechsler Preschool and Primary Scale of Intelligence-Revised [WPPSI-R] [23], or Mullen Scales of Early Learning [24]), academic achievement (Wechsler Individual

Achievement Test-II-Abbreviated [WIAT-II-A] [25]), attention regulation (Conners' Continuous Performance Test-II [CPT-II] [26] or Conners' Kiddie Continuous Performance Test [K-CPT] [27]), executive functioning (Behavior Rating Inventory of Executive Function [BRIEF] [28]), and behavior (Behavior Assessment System for Children, Second Edition [BASC-2] [29]).

The WASI is a standardized measure of intelligence for patients aged 6 years and over. The WPPSI-R and Mullen scales are standardized measures of intelligence which are used in CKiD for children aged 30 months to 5 years and aged 29 months or below, respectively. The WIAT-II-A is a standardized measure of achievement for children aged 6 years and above. WASI, WPPSI-R, Mullen, and WIAT-II-A scores are reported as standardized scores with mean 100 and standard deviation (SD) 15; higher scores indicate better performance in these measures.

The CPT-II is a computerized measure of attention for ages 6 years and up that requires the individual to touch the mouse or space bar in response to visual stimuli. Scores are generated for errors of omission, errors of commission, hit reaction time, variability (level of within-subject consistency in response speed), and detectability (ability to discriminate between target and non-target stimuli). Errors of omission and variability are considered the primary measures of inattention. The K-CPT is a similar measure of attention used in children 4 to 5 years of age that requires shorter testing time. The BRIEF is a parent-completed scale for children down to age 6 years, and generates a behavior regulation index (BRI), metacognition index (MI), and a global executive composite (GEC). A preschool version of BRIEF (BRIEF-P) for children down to age 2 years generates different indexes than the BRIEF (inhibitory self-control, flexibility, and emergent metacognition rather than BRI and MI), but also generates a GEC score which can be compared to that from the version of the BRIEF for older children. The BASC consists of parent-reported behavior scales for children down to age 2 years and a self-report for children aged 8 years and above. Scores for the CPT-II, K-CPT, BRIEF, and BASC tests are reported as T-scores, with a mean of 50 and SD of 10. Higher scores on these tests indicate worse performance, except for the adaptive skills and personal adjustment domains within the BASC. Order effects were controlled via counterbalancing blocks of tasks. All of the tasks were administered/supervised by a licensed psychologist.

Normative data for all tests are based on large national samples representative of the United States population. Raw scores are converted to standardized scores or T-scores based on age-specific norms.

For this study, the first available assessment for a particular instrument (e.g. BRIEF, CPT-II) in each patient was used for analysis, regardless of the number of study visits. BRI and MI scores were used from the BRIEF for older children, and GEC scores were pooled from the standard and preschool versions of the BRIEF.

Clinical Variables

GFR is measured in CKiD by plasma disappearance of iohexol (iGFR) at study entry, one-year follow-up, and every two years thereafter [30]. Casual blood pressure (BP)

measurements are obtained at each study visit. Ambulatory BP monitoring (ABPM) is performed one year after study entry and every two years thereafter. Blood tests including complete blood count, renal panel, and cystatin C are obtained at study entry and yearly thereafter. Demographic information and medical history (including medication use) are recorded using standardized forms at each study visit. Clinical variables used in the current study were ieGFR from the baseline visit, and first available measures for the remaining variables.

Data Analysis

Demographic and clinical characteristics for ARPKD subjects and controls were reported as median values with interquartile range (IQR), or frequencies and percentages, as appropriate. Scores for neurocognitive tests were reported as medians with IQR for ARPKD subjects and controls. "At-risk" scores for all neurocognitive tests were defined as 1 SD worse than the mean, and frequencies/percentages of at-risk patients were reported for each group. Comparison of clinical characteristics of ARPKD subjects and controls was performed using the Wilcoxon rank-sum test for continuous variables, and using Fisher's exact test for proportions. Comparison of group medians for neurocognitive variables was carried out using quantile regression and adjusted for maternal education, a known confounder for neurocognitive outcomes [8, 31]. Due to the small sample size, no other covariates were included. Unadjusted comparisons were performed for the proportions of at-risk patients for each neurocognitive variable. Data analysis was carried out using SAS 9.2. The significance level for all data analyses was set at $p = 0.05$.

Results

Baseline Characteristics

A total of 23 children with ARPKD were enrolled in CKiD, of whom 22 had completed their initial study visit and were used for analysis. The control group consisted of 44 children with aplastic/hypoplastic/dysplastic kidneys (drawn from a total of 144 potential subjects) matched based on baseline ieGFR, age at study entry, and age at diagnosis. Measured GFR (iGFR) was available in 20 of 22 ARPKD patients (91%) and in 42 of 44 controls (95%). Table 1 shows the clinical and demographic characteristics of the ARPKD subjects and controls. A higher proportion of children in the ARPKD group were of non-African American race, but this difference was not statistically significant ($p = 0.15$). A higher percentage of ARPKD patients were of Hispanic ethnicity compared to controls ($p = 0.03$). Levels of maternal education were slightly higher in the ARPKD group, but this difference was not statistically significant ($p = 0.41$). Hemoglobin levels were lower in the ARPKD group compared to controls (11.7 g/dL *versus* 12.7 g/dL, $p = 0.003$). There were no significant group differences in the frequency of parent-reported attention deficit hyperactivity disorder (ADHD) or learning disability (LD).

The control group had higher proportions of children with history of low birth weight (LBW) and seizure disorder, but these differences were not statistically significant ($p = 0.25$ for both). However, given the known neurocognitive impact of LBW and seizures[8], we performed additional analysis of selected neurocognitive measures in a second control group

to verify our findings from the first control group. The second control group also consisted of 44 children with aplastic/hypoplastic/dysplastic kidneys (drawn from the same pool of 144 potential subjects), but was matched for prevalence of LBW and seizures, in addition to the original matching factors. Baseline characteristics of the second control group are shown in Supplementary Table 1.

Performance on Neurocognitive Measures

Intellectual Functioning—Scores for Composite IQ, Verbal IQ (VIQ), and Performance IQ (PIQ) on the WASI, WPPSI-R, or Mullen scales were within normal range for both ARPKD subjects and controls. Composite IQ was higher for ARPKD subjects compared to controls (ARPKD: median 106, IQR 99 to 112; controls: median 94, IQR 85 to 105); however, the difference was not statistically significant after adjusting for maternal education (p = 0.09). Similarly, group differences for VIQ and PIQ were not statistically significant after adjusting for maternal education (Table 2). No ARPKD subjects were at-risk (i.e. 1 SD worse than the mean) for Composite IQ or VIQ, compared to more than 30% of controls (p = 0.003 for both, not adjusted for maternal education). The proportions at risk on PIQ were not significantly different. Findings were similar in the second control group (Supplementary Table 2).

Academic Achievement—Total achievement scores in the WIAT-II-A were higher for ARPKD subjects than for controls (ARPKD: median 109, IQR 93 to 117; controls: median 93, IQR 87 to 105). Again, the differences were not statistically significant after adjusting for maternal education. Findings were similar for the numeric operations, spelling, and word reading subscales. Comparison of the proportion of children with at-risk scores showed no significant differences between ARPKD subjects and controls. These findings were replicated in the second control group (Supplementary Table 2).

Attention Regulation—There were no statistically significant differences in median CPT-II or K-CPT scores for any domain (errors of omission, errors of commission, hit reaction time, variability, and detectability) between ARPKD subjects and either of the two control groups. In addition, there were no significant differences in the proportion of children with an at-risk score in any of the domains (Table 2 and Supplementary Table 2).

Executive Functioning—Global executive composite (GEC) scores were pooled from the BRIEF and BRIEF-P, and were comparable between ARPKD patients and controls (ARPKD: median 51, IQR 47 to 57; controls: median 54, IQR 45 to 66; p = 0.59). The BRI and MI summary scales from the BRIEF were also similar between the two groups, with each of these summary scores falling within the average range. There were no significant differences in the proportion of at-risk scores for GEC, BRI, or MI (Table 2), with percentages ranging from 2% to 3% for the ARPKD group. Findings were similar in the second control group (Supplementary Table 2).

Behavior—There were no significant differences in median scores or the proportion of at-risk scores between ARPKD patients and controls for the BASC summary scales of externalizing and internalizing problems, overall behavioral symptoms, and adaptive skills.

There were fewer results available for analysis for the BASC self-report ($n = 6$ for ARPKD, and $n = 22$ for controls) since it is only completed by children 8 years of age and older and its use was discontinued in CKiD in 2008. There were no statistically significant differences in median scores for any of the BASC self-report subscales (after adjusting for maternal education). Unadjusted comparison of the proportion of at-risk scores revealed a greater proportion of ARPKD patients with at-risk scores for hyperactivity/inattention compared to controls (4/6 or 67% of ARPKD subjects *versus* 2/22 or 9% of controls, p = 0.01). However, these results are difficult to interpret given the small number of patients (Table 2).

Systemic Hypertension

To standardize the comparison of BP values between subjects of different gender, age, and height, BP index values (defined as subject's BP divided by 95th percentile BP for gender, age, and height [32]) were used. For casual BP measurements, median SBP index was similar in ARPKD patients and controls, and DBP index was slightly lower in ARPKD patients compared to controls (p = 0.05) (Table 1). There was no significant difference between ARPKD subjects and controls in the proportion of children characterized as having either elevated BP blood pressure (SBP or DBP ≥ 90th percentile) or hypertension (SBP or DBP ≥ 95th percentile). Comparison of ambulatory BP monitoring results between ARPKD subjects and controls showed no significant difference in the proportion of children with elevated BP load (defined as ≥ 25% BP readings over 95th percentile) [33, 34]. These results are summarized in Table 3.

Despite relatively similar blood pressure values between ARPKD subjects and controls, there were significant differences in the number of antihypertensive medications required to achieve those levels of BP control. Overall, 68% of ARPKD patients required two or more antihypertensive medications, compared to only 9% of controls (p < 0.0001). These differences persisted even after excluding angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) which may sometimes be used for their potential renoprotective rather than antihypertensive effects (Table 4).

Discussion

The major strength of this study is that it is the first to systematically investigate neurocognitive outcomes in children with ARPKD. The CKiD study represents a unique resource given the comprehensive nature of neurocognitive assessments performed. Although our study reports on a relatively small number of patients, this represents the largest group of ARPKD patients to date to undergo such detailed neurocognitive phenotyping.

The primary aim of this study was to determine whether there are disease-specific effects of ARPKD on neurocognition. Overall, the results of this study provide some reassurances to parents and caregivers of children with ARPKD. Functioning in domains of intelligence, academic achievement, attention regulation, executive functioning, and behavior of children with ARPKD in this cohort was generally similar to that of the control group. In both the ARPKD and control groups, scores in all domains were within the average range based on age-specific normative data from large national samples. In a previous study of children

aged 6 to 16 years in the CKiD cohort, mean scores for all neurocognitive measures were also found to fall within age-appropriate expectations [8]. However, a disproportionate number of patients in that report demonstrated risk for neurocognitive dysfunction (defined as scores > 1 SD below mean), particularly in domains of executive functioning. Similarly, in the current study, higher than expected proportions of at-risk scores were observed in some measures of attention (CPT-II/K-CPT), executive function (BRIEF), and behavior (BASC). However, other than the hyperactivity/inattention subscale in the small number of patients completing the BASC self-report, there was no evidence of increased risk in patients with ARPKD compared to the control group. While our analysis did not explicitly preserve matching between individual ARPKD subjects and their controls, in most matched studies this does not affect inference. A sensitivity analysis that incorporated the matching explicitly (results not shown) revealed inferences comparable to our main analysis. Given the association of hypertension with adverse neurocognitive outcomes [12–16], and previous reports of high prevalence of severe hypertension in ARPKD, we also sought to characterize blood pressures in our cohort. Overall rates of elevated BP, hypertension, and elevated ABPM load were similar between ARPKD patients and the control group. However, examination of the number of antihypertensive medications required revealed significant differences between ARPKD patients and controls, even after exclusion of ACEi/ARBs. This may indicate that patients with ARPKD have more severe underlying hypertension requiring more aggressive pharmacotherapy. The effect of this difference on neurocognitive results in the current study is difficult to discern. In patients with primary hypertension, antihypertensive therapy has been shown to improve executive function [19]. In a prior study in the CKiD cohort, however, higher BP was associated with lower performance IQ regardless of antihypertensive medication treatment [16]. Given that the effects of hypertension on neurocognitive test performance can be subtle, the relatively small sample size in this study may not be sufficient to detect such effects.

Aside from the comprehensive nature of the neurocognitive assessments in CKiD, another strength of this study is the detailed clinical characterization of patients, including the availability of measured GFR in the vast majority of patients. There are, however, limitations to our study. While this study is the first to comprehensively analyze neurocognition in ARPKD, it is limited by the relatively small number of ARPKD patients enrolled in CKiD. Despite this limitation, this is the largest cohort of ARPKD patients ever reported to undergo comprehensive neurocognitive evaluation, making our study an important first step in addressing this issue. Our relatively small sample size may, however, have decreased our ability to detect subtle differences in neurocognitive function between the ARPKD and control groups. Since our study was exploratory in nature, we chose not to adjust our analyses for multiple comparisons in order to maximize our ability to detect small differences.

To determine whether ARPKD has disease-specific effects on neurocognition, we chose to compare children with ARPKD with matched controls with renal aplasia/hypoplasia/ dysplasia. A limitation of this approach, however, is that we could not determine how ARPKD subjects compare to age-matched healthy controls or to children with other CKD diagnoses. Further studies are therefore needed to replicate these data with other comparison groups, including typically-developing age-matched controls.

Another limitation of our study relates to the generalizability of our results to the ARPKD population as a whole. Given the relatively narrow inclusion criteria for the CKiD study (e.g. only children with mild-to-moderate CKD and exclusion of organ transplant recipients), our findings may not be representative of the full range of deficits that could occur in children with more severe manifestations of ARPKD. In addition, while the neurocognitive assessments performed in CKiD are very comprehensive, they do not cover all aspects of neurobehavioral health. For example, the clinical experiences of the co-authors (unpublished) suggest the presence of mood and anxiety symptoms/disorders in children with ARPKD. To further investigate these observations, different evaluation techniques (e.g., structured interviews, specific measures of psychopathology and emotional status) may be necessary to detect such clinical manifestations. Therefore, further studies that also examine other aspects of neurobehavioral health are needed in a broader range of ARPKD patients to address these questions.

In summary, this study shows that despite their potentially increased risk, children with ARPKD and mild-to-moderate CKD appear to have neurocognitive functioning comparable to children with other causes of CKD. This study confirms that children with ARPKD appear to have more severe underlying hypertension than their CKD counterparts, as evidenced by greater need for antihypertensive therapy. Longitudinal studies would be required to discern the effects of underlying hypertension and antihypertensive therapy on neurocognitive outcomes in this population. While the known effects of CKD and hypertension on neurocognition should prompt vigilance in clinicians caring for children with ARPKD, the results of our study indicate that children with ARPKD do not demonstrate evidence of disease-specific neurocognitive dysfunction, at least in this cohort of children with mild-to-moderate kidney disease. Strategies to facilitate routine neurodevelopmental surveillance of children with ARPKD will address the presence or later emergence of neurobehavioral difficulties in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of ARPKD subjects and controls

Characteristic	ARPKD Subjects ($N = 22$)	Controls ($N = 44$)	P
Age at study entry (years)[a]	7.5 (4.8, 9.4)	7.6 (6.1, 9.8)	0.70
2 to 5 years[b]	9 (41%)	11 (25%)	0.33
6 to 8 years[b]	6 (27%)	19 (43%)	
9 years[b]	7 (32%)	14 (32%)	
Male gender[b]	10 (45%)	22 (50%)	0.79
Race[b]			
Non-African American	21 (95%)	35 (80%)	0.15
African American	1 (5%)	9 (20%)	
Hispanic ethnicity	8 (36%)	5 (12%)	0.03
Maternal education (more than high school)[b]	17 (77%)	29 (66%)	0.41
Age at CKD diagnosis, years[a]	0.08 (0.00, 0.33)	0.01 (0.00, 1.08)	0.65
iGFR (mL/min/1.73 m²)[a]	38.7 (28.3, 54.6)	37.7 (29.2, 54.5)	0.91
eGFR (mL/min/1.73 m²)[a]	39.2 (30.5, 55.3)	41.0 (33.3, 51.9)	0.77
Low birth weight (<2500 g)[b]	4 (18%)	15 (35%)	0.25
Learning disability (parent report)[b]	0 (0%)	3 (7%)	0.54
ADHD (parent report)[b]	0 (0%)	1 (2%)	1.00
Seizures[b]	1 (5%)	7 (16%)	0.25
Hemoglobin (g/dL)[a]	11.7 (10.8, 12.4)	12.7 (12.0, 13.7)	0.003
SBP index[a]	0.93 (0.84, 1.02)	0.90 (0.80, 0.99)	0.67
DBP index[a]	0.76 (0.71, 0.81)	0.84 (0.73, 0.94)	0.05

ADHD, attention deficit hyperactivity disorder; ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; GFR, glomerular filtration rate, determined by plasma iohexol disappearance (iGFR) or by estimation using CKiD estimation equations (eGFR) [35];

SBP, systolic blood pressure; DBP, diastolic blood pressure. SBP/DBP index defined as subject's BP divided by 95th percentile BP for gender, age, and height. [32]

[a] Median (interquartile range)

[b] Number (% of total)

Table 2

Comparison of neurocognitive measures for autosomal recessive polycystic kidney disease (ARPKD) subjects and controls

Neurocognitive Domain (Test)	ARPKD Subjects		Controls		p^b
	N	Median score (IQR) At-risk^a, n (%)	N	Median score (IQR) At-risk^a, n (%)	
Intellectual Functioning (WASI, WPPSI-R, or Mullen)					
Composite IQ	21	106 (99, 112) 0 (0%)	42	94 (85, 105) 13 (31%)	0.09 0.003
Verbal IQ	21	108 (97, 114) 0 (0%)	41	94 (82, 108) 13 (32%)	0.10 0.003
Performance IQ	21	102 (96, 107) 1 (5%)	41	96 (88, 101) 7 (17%)	0.07 0.25
Academic Achievement (WIAT-II-A)					
Total Achievement	9	109 (93, 117) 1 (11%)	28	93 (87, 105) 6 (21%)	0.13 0.66
Numeric Operations	9	109 (97, 123) 1 (11%)	28	95 (84, 106) 8 (29%)	0.20 0.40
Spelling	9	106 (101, 114) 1 (11%)	28	98 (91, 105) 4 (14%)	0.26 1.00
Word Reading	9	104 (97, 109) 1 (11%)	28	95 (88, 108) 6 (21%)	0.33 0.66
Attention Regulation (CPT-II or K-CPT)					
Variability	18	57 (48, 60) 7 (39%)	38	57 (46, 64) 17 (45%)	0.85 0.78
Errors of Omission	18	48 (44, 49) 2 (11%)	38	50 (45, 60) 10 (26%)	0.38 0.30
Errors of Commission	18	50 (38, 58) 4 (22%)	38	52 (45, 61) 11 (29%)	0.64 0.75
Hit reaction Time	18	52 (41, 55) 2 (11%)	38	55 (45, 59) 9 (24%)	0.44 0.47
Detectability	18	52 (47, 56) 2 (11%)	38	52 (49, 59) 9 (24%)	1.00 0.47
Executive Functioning (BRIEF)					
Behavior Regulation Index	14	50 (47, 58) 3 (21%)	32	50 (45, 62) 10 (31%)	1.00 0.72
Metacognition Index	14	53 (46, 56) 2 (14%)	31	54 (44, 66) 10 (32%)	0.66 0.29

Neurocognitive Domain (Test)	ARPKD Subjects		Controls		P^b
	N	Median score (IQR) At-risk^a, n (%)	N	Median score (IQR) At-risk^a, n (%)	
Global Executive Composite	20	51 (47, 57) 3 (15%)	41	54 (45, 66) 13 (32%)	0.59 0.22
Behavior (BASC Parent Report)					
Externalizing Problems	21	49 (44, 56) 7 (33%)	43	49 (44, 55) 15 (35%)	1.00 1.00
Internalizing Problems	21	53 (50, 61) 3 (14%)	43	54 (46, 64) 6 (14%)	1.00 1.00
Behavioral Symptoms	21	50 (47, 56) 4 (19%)	43	53 (46, 60) 11 (26%)	0.18 0.76
Adaptive Skills	21	49 (42, 54) 5 (24%)	43	44 (37, 52) 15 (35%)	0.19 0.41
Behavior (BASC Self-Report)					
School Problems	7	48 (41, 73) 2 (29%)	22	48 (42, 51) 4 (18%)	0.88 0.61
Internalizing Problems	6	48 (41, 50) 1 (17%)	22	47 (43, 51) 0 (0%)	0.84 0.21
Hyperactivity/Inattention	6	66 (51, 73) 4 (67%)	22	51 (45, 57) 2 (9%)	0.50 0.01
Emotional Symptoms	6	49 (43, 53) 1 (17%)	22	48 (41, 51) 0 (0%)	0.39 0.21
Personal Adjustment	6	47 (43, 56) 0 (0%)	22	53 (45, 58) 3 (14%)	1.00 1.00

Wechsler Abbreviated Scales of Intelligence (WASI), Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), and Mullen Scales of Early Learning intelligence quotients (IQ) and Wechsler Individual Achievement Test-II-Abbreviated (WIAT-II-A) are reported as standard scores with means of 100 and a standard deviation of 15. Higher scores indicate better performance for these assessments. Conners' Continuous Performance Test-II (CPT-II), Conners' Kiddie Continuous Performance Test (K-CPT), Behavior Rating Inventory of Executive Functions (BRIEF), and Behavior Assessment System for Children, Second Edition (BASC–2) are reported as standard T-scores with a mean of 50 and a standard deviation of 10; higher scores indicate worse performance except for the adaptive skills and personal adjustment domains within BASC.

^{a}"At-risk" score defined as 1 standard deviation worse than the standard mean

^{b}P-values for comparison of group medians are all adjusted for maternal education. P-values for comparison of proportion of subjects with "at-risk" scores are unadjusted.

Table 3

Comparison of blood pressure parameters for ARPKD subjects and controls

BP parameter	ARPKD Subjects		Controls		P
	N	n (%)	N	n (%)	
Elevated SBP[a]	22	8 (36%)	43	13 (30%)	0.78
Elevated DBP[a]	22	4 (18%)	42	10 (24%)	0.76
Systolic hypertension[b]	22	6 (27%)	43	10 (23%)	0.77
Diastolic hypertension[b]	22	1 (5%)	42	7 (17%)	0.25
Systolic ABPM load[c] 25%	16	6 (38%)	27	7 (26%)	0.50
Diastolic ABPM load[c] 25%	16	2 (13%)	27	6 (22%)	0.69

ARPKD, autosomal recessive polycystic kidney disease; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; ABPM, ambulatory BP monitoring

[a] Elevated BP = SBP/DBP 90th percentile

[b] Hypertension = SBP/DBP 95th percentile

[c] ABPM load = % of readings 95th percentile [33, 34]

Table 4

Comparison of antihypertensive medication use in ARPKD subjects and controls

Number of antihypertensive medications	ARPKD Subjects *n* (%)	Controls *n* (%)	*P*
All			
0	3 (14%)	26 (59%)	< 0.0001
1	4 (18%)	14 (32%)	
2 or more	15 (68%)	4 (9%)	
Excluding ACEi and ARB			
0	8 (36%)	38 (86%)	< 0.0001
1	8 (36%)	6 (14%)	
2 or more	6 (27%)	0 (0%)	

ARPKD, autosomal recessive polycystic kidney disease; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers