Kidney International, Vol. 68 (2005), pp. 2218–2224

Autosomal-dominant polycystic kidney disease in infancy and childhood: Progression and outcome[1]

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Autosomal-dominant polycystic kidney disease in infancy and childhood: Progression and outcome.

Background. The natural history of autosomal-dominant polycystic kidney disease (ADPKD) has not been well described in children and infants.

Methods. The present study analyzed the characteristics of 46 ADPKD children diagnosed before 18 months of life (VEO) and 153 children diagnosed between 18 months of age and 18 years of age (non-VEO).

Results. VEO children had more cysts and larger renal volumes than non-VEO children when adjusted for age. In both VEO and non-VEO children, the presence of signs or symptoms at the time of diagnosis as well as the presence of hematuria or proteinuria at the study visit were associated with larger renal volumes. Children diagnosed early (VEO) or diagnosed due to signs or symptoms were also more likely to have high blood pressure. Two VEO children and no non-VEO children reached end-stage renal disease during follow-up.

Conclusion. In contrast to many published case reports suggesting the occurrence of early end-stage renal disease in VEO children, the results of the present study were much more optimistic. Over 90% of the VEO children maintained preserved renal function well into childhood.

Autosomal-dominant polycystic kidney disease (ADPKD) is the most frequent life-threatening hereditary disease [1], affecting from 1 in 500 to 1 in 1000 individuals in the United States and Europe. It accounts for 4.4% of end-stage renal disease (ESRD) in the United States [2]. Although ADPKD often is considered a disease of adults, it is clear that the disease begins in childhood. Renal cysts in children with ADPKD have been associated with wide clinical spectra, ranging from totally asymptomatic patients to those who present as newborns with massive renal enlargement, hypertension, oliguria, and pulmonary hypoplasia [3]. While many case reports of symptomatic, severe disease in early childhood have been published [4, 5], very few cross-sectional [6] and longitudinal studies [7] have been performed on the rate of progression and the factors associated with progression in children.

In adults, factors other than the culprit gene mutation alone contribute to the course of progression of the renal failure. The following variables have been independently associated with progression to ESRD: the *PKD1* compared to the *PKD2* gene mutation, younger age at diagnosis, male gender, hypertension, increased left ventricular mass, hepatic cysts in women, three or more pregnancies, gross hematuria, urinary tract infections in men, and renal size expressed as renal volume [8]. However, disease progression and outcome have not been fully understood in the patients who are diagnosed in the early months of life.

Given the frequency of ADPKD in the population and the widespread use of imaging techniques in pregnancy, it is likely that more fetuses and young children will be identified with ADPKD. In the previous case reports the ADPKD patients who have been diagnosed in fetal life or infancy were considered to have a high rate of mortality and severe complications [9–11]. The number of ADPKD subjects in these reports, however, was small and the duration of follow-up brief. We therefore undertook a comprehensive prospective analysis of the natural history of 46 ADPKD children who were diagnosed either in utero or within the first 18 months of life [i.e., very early onset (VEO)], and 153 ADPKD children who were diagnosed between 18 months and 18 years of age.

METHODS

Since 1985, 895 subjects with ADPKD from 419 families participated in ADPKD studies at the University of Colorado Health Sciences Center (UCHSC). All parents were asked to have their children participate in an ongoing longitudinal study. In addition, children with known

[1] **See Editorial by Steinman, p. 2398.**

Key words: ADPKD, childhood, disease progression.

Received for publication March 30, 2005
and in revised form May 12, 2005
Accepted for publication June 1, 2005

ADPKD were referred to the UCHSC for participation in the study. The children and their affected parent were asked to return for follow-up visits every three years. Parents provided informed consent, and all children over the age of seven years provided an assent.

All children and their affected parent were admitted to the Pediatric Clinical Research Center at The Children's Hospital or to the General Clinical Research Center at University Hospital in Denver for a 48-hour stay. All children and parents underwent a standard history, physical examination, blood sampling for complete blood count, routine chemistries and gene linkage analysis, and collected 24-hour urine specimens for creatinine, electrolytes, and protein as previously described [12].

Blood and urinary chemistry determinations were performed by the Clinical Laboratories of University Hospital or The Children's Hospital. Urinary protein concentrations were measured using the Coumassie blue dye-binding method [13]; urinary albumin concentrations were measured since 1994 using a standard radioimmunoassay (Diagnostics Products, Los Angeles, CA, USA). Overt proteinuria was defined as urinary protein excretion greater than 4 mg/m^2 per hour [14]. Glomerular filtration rate (GFR) was calculated by the Schwartz formula GFR $= (k \times L)/P_{Cr}$, where L is the length (height) of the child in cm, P_{Cr} the plasma creatinine concentration in mg/dL, and $k = 0.45$ for children younger than two years, $k = 0.55$ for children age 2 to 12 years and for girls age 13 to 18 years, and $k = 0.70$ for boys age 13 to 18 years old [15].

During their two-day hospital stay, the children had multiple blood pressure measurements obtained (mean 14, range 2 to 20); these were taken on the dominant arm with an automatic device (Dynamap; Critikon, Inc., Tampa, FL, USA) in the sitting position using a cuff appropriate for the child's upper arm circumference. These blood pressures were compared with established standards of blood pressures for children of a given age, gender, and height [16]. Hypertension was defined as 50% or more of either systolic or diastolic in-house blood pressures above the 95th percentile for age-, gender-, and height-matched children, or being on antihypertensive therapy, whereas normal blood pressure was defined as more than 50% of both systolic and diastolic blood pressures at or below the 95th percentile.

All children had abdominal ultrasonography as previously described [17]. Abdominal ultrasound was performed with a high-resolution real-time scanner (Acuson 1.28 EXP with a 3.5 or 5.0 MHz transducer; Acuson, Malvern, PA, USA). The children were considered to have ADPKD if they had a family history and at least a single cyst by ultrasonography. Renal cysts were counted, if possible, or tabulated as 0, 1–5, 6–15, or greater than 15. The largest cyst in each kidney was reported, as well as the predominant cyst size (<2 cm, 2–5 cm, or >5 cm) and whether the cysts were uniform or variable in size. Renal volume was calculated as a modified ellipse from the measurements obtained by ultrasound [6]. Because in this study only a small number of children had markedly asymmetric kidneys, that is, one kidney having more than double the volume of the other, the mean renal volume was calculated for each child as the average of the two kidneys. Renal volumes were determined at every visit (on average every 3 years) for all affected and unaffected children. Echocardiograms were performed as previously described [18]. Follow-up data on hypertension and ESRD were sought on all children by questionnaire or phone call between December 2004 and early 2005.

The data were analyzed using SAS (Statistical Analysis System; Cary, NC, USA). Ages are presented as the mean ± standard deviation. P values < 0.05 were considered significant; P values < 0.10 are reported. T tests were used to compare means between groups. Age-adjustment using analysis of covariance (ANCOVA) was performed for all quantitative variables; age-adjusted data are presented as the least squares mean ± the standard error. Log transformations were used for renal growth rate because of skewed distributions. Qualitative parameters were compared between groups using chi-square analysis.

RESULTS

Forty-six subjects from 40 families were diagnosed with ADPKD by imaging within the first 18 months of life. Among them, 10 were diagnosed due to signs or symptoms, including the physical finding of an abdominal mass ($N = 8$) or the symptom of acute pyelonephritis ($N = 2$). The remaining 36 subjects were asymptomatic at the time of diagnosis; they were diagnosed by renal ultrasound screening in families with a history of ADPKD ($N = 30$, 14 were diagnosed in utero) or as an incidental finding on a routine prenatal ultrasound ($N = 6$). One hundred fifty-three subjects from 109 families were diagnosed by imaging after age 18 months but before age 18 years (non-VEO). Among them, 41 were diagnosed due to signs or symptoms, including pain ($N = 12$), hypertension ($N = 8$), urinary tract infection ($N = 6$), hematuria ($N = 7$), kidney stones ($N = 2$), frequency ($N = 2$), and one subject each for abdominal mass, acute pyelonephritis, enuresis, and stress incontinence. One hundred and seven non-VEO children were diagnosed due to screening; for 5 non-VEO children the data on reason for diagnosis are missing. Seventeen of the non-VEO children had negative renal ultrasounds prior to the ultrasound at which they received the diagnosis, one child at age 14. All children were born between 1975 and 1997. Fifteen families had both a VEO and a non-VEO child.

Table 1. Characteristics of VEO and non-VEO patients at last clinical research center visit

	VEO ($N = 46$)	non-VEO ($N = 153$)	P value
Age at last visit *years* ± *SD*	9.5 ± 5.8	14.5 ± 4.3	<0.0001
Gender % *male*	46	46	NS
Affected mother %	67	58	NS
Serum creatinine *mg/dL*[a]	0.9 ± 0.05	0.8 ± 0.03	<0.005
Creatinine clearance *mL/min/1.73m*^{2}[a]	103 ± 4	116 ± 2	<0.005
Schwartz GFR *mL/min/1.73m*^{2}[a]	113 ± 4	129 ± 2	<0.005
Urinary protein excretion *mg/24 hr*[a]	192 ± 29	158 ± 13	NS
Overt proteinuria %	45	34	NS
Urinary osmolality *mOsm/kg*[a]	725 ± 50	858 ± 20	<0.05
Hypertensive %	43	29	0.06
Left ventricular mass index *g/m*^{2}[a]	77 ± 3	72 ± 1	0.07
Liver cyst(s) present on ultrasound %	2	1	NS
History of inguinal hernia %	18	5	<0.01
History of umbilical hernia %	9	1	<0.05
Family history of intracranial aneurysm %	24	32	NS
History of gross hematuria %	15	15	NS

[a]Age-adjusted mean ± SEM.

Characteristics of VEO versus non-VEO children

Table 1 shows the characteristics at the last clinical research center visit of the VEO and non-VEO children. The VEO patients were significantly younger. [Because VEO patients were diagnosed in the early months of life, they were also younger at their first visit (5.5 ± 5.4 vs. 10.4 ± 4.5 years, $P < 0.0001$)]. The VEO children had higher serum creatinine concentrations, lower creatinine clearance and GFR, lower overnight urinary osmolality, and excreted more protein in their urine. The difference in protein excretion, however, was not significant. Hypertension was more prevalent and left ventricular mass indices were greater in VEO subjects, although the differences did not quite reach statistical significance. The VEO patients had more hernias. Another finding was that VEO patients, at comparable ages, had a higher percentage, with 20 or more renal cysts ($P < 0.05$) (Fig. 1). Figure 2 depicts the age-adjusted renal volumes, which were larger in the VEO than in the non-VEO children (370 ± 38 vs. 224 ± 20 cm^3, $P < 0.005$). At their last visit, 54% of VEO and 29% of non-VEO children had too many cysts to count. The predominant cyst size was less than 2 cm in over 90% of the children (both VEO and non-VEO), and the cysts tended to be uniform in size. The largest cyst was usually less than 3 cm (mean 2.7 cm, range 0.3–8.9 cm, interquartile range 1.4–3.7 cm) and increased slowly over time (<0.2 cm/year).

Diagnosis due to signs or symptoms versus screening

Clinical characteristics of both VEO and non-VEO children who were diagnosed due to signs or symptoms are compared with characteristics of children diagnosed due to screening in Table 2. In both VEO and non-VEO groups, children diagnosed due to signs or symptoms had higher age-adjusted serum creatinine levels, lower age-adjusted creatinine clearances and GFRs, and a greater frequency of hypertension than children diagnosed due to screening. Mean age-adjusted renal volumes of the groups are shown in Figure 3.

Relationship between hematuria and proteinuria with renal volume in ADPKD children

Both hematuria and overt proteinuria were associated with larger renal volumes in both VEO and non-VEO children (Fig. 4).

Hypertension and ESRD at follow-up

Comparisons between VEO and non-VEO children at the most recent follow-up demonstrated significantly more hypertension in the VEO than in the non-VEO children (52% vs. 32%, $P < 0.05$), and between non-VEO children diagnosed due to signs or symptoms versus non-VEO children diagnosed due to screening (VEO 60% vs. 50%, $P =$ NS; non-VEO 59% vs. 23%, $P < 0.0001$). ESRD had occurred in only 2 of the 46 VEO children (4.3%, at ages 3.5 and 4); the mean age of the VEO children at follow-up was 13.4 ± 6.9 years (range 1 to 29 years). None of the non-VEO children developed ESRD by a mean age of 16.2 ± 5.2 years (range 2 to 27 years). The two VEO children who reached ESRD were diagnosed due to signs or symptoms (abdominal mass).

Increases in renal volume over time

Overall, renal volume growth rate increased with age with the highest growth rate during puberty (age at first visit 0 to <5 years: 8.7 ± 1.2 cm^3/year; 5 to <10 years 16.8 ± 1.2 cm^3/year; 10 to <15 years: 25.0 ± 1.2 cm^3/year; $P < 0.0001$). There was a near significant difference in renal volume growth rate between VEO and non-VEO children (age-adjusted mean ± SEM VEO 18.6 ± 1.2 vs. non-VEO 12.7 ± 1.1, $P = 0.06$).

DISCUSSION

Over the past two decades, it has become clear that ADPKD is a significant entity in childhood, and clinical characteristics of ADPKD children have been reported [5–7, 18]. The progression of ADPKD to ESRD and the presence of other complications are highly variable in children [6] and are not completely understood in the early years of life. In the present study, 46 subjects from 40 families whose disease had been diagnosed within the first 18 months of life (VEO) were evaluated and compared with those children who were diagnosed between 18 months and 18 years of age (153 subjects).

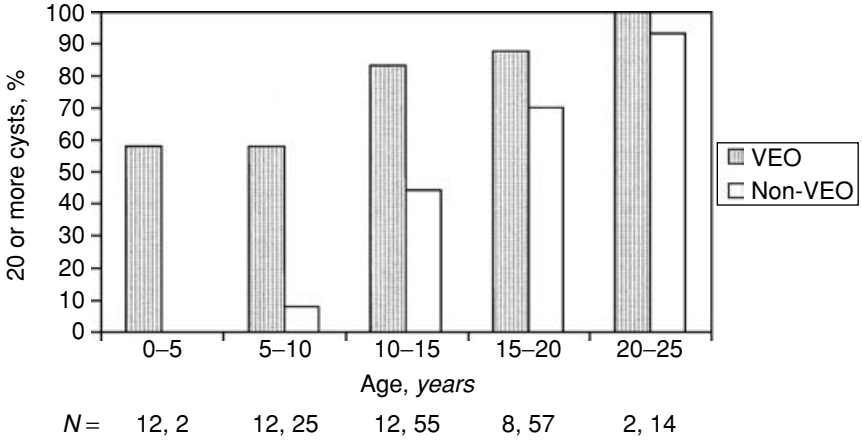

Fig. 1. A greater percentage of VEO children had 20 or more renal cysts bilaterally on ultrasound than non-VEO children at the last clinical research center visit (overall $P < 0.05$).

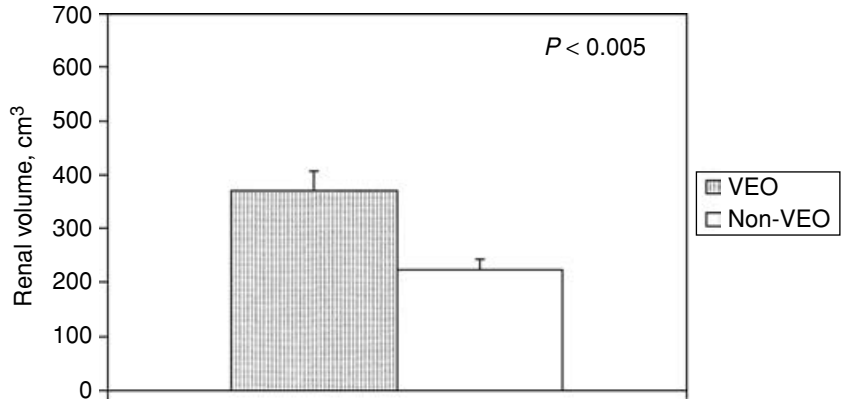

Fig. 2. VEO children had larger (age-adjusted) renal volumes than non-VEO children at the last clinical research center visit.

Table 2. Characteristics of VEO and non-VEO patients, diagnosed due to signs or symptoms (SY) or diagnosed for screening (SC), at last clinical research center visit

	VEO SY ($N = 10$)	VEO SC ($N = 36$)	*P* value VEO	non-VEO SY ($N = 41$)	non-VEO SC ($N = 107$)	*P* value non-VEO
Age at last visit *years* ± *SD*	11.6 ± 6.1	8.9 ± 5.7	NS	15.2 ± 4.4	14.3 ± 4.1	NS
Gender % *male*	50	44	NS	39	48	NS
Affected mother %	60	69	NS	54	61	NS
Serum creatinine *mg/dL*[a]	1.3 ± 0.16	0.6 ± 0.08	<0.001	0.8 ± 0.04	0.8 ± 0.02	NS
Creatinine clearance *mL/min/1.73m*^{2}[a]	93 ± 10	111 ± 6	NS	107 ± 3	119 ± 2	<0.005
Schwartz GFR *mL/min/1.73m*^{2}[a]	96 ± 12	125 ± 6	<0.05	118 ± 4	131 ± 2	<0.01
Urinary protein excretion *mg/24 hr*[a]	219 ± 68	141 ± 39	NS	164 ± 25	166 ± 15	NS
Overt proteinuria %	50	43	NS	42	32	NS
Urinary osmolality *mOsm/kg*[a]	799 ± 143	730 ± 63	NS	850 ± 52	863 ± 21	NS
Hypertensive %	60	39	NS	59	19	<0.0001
Left ventricular mass index *g/m*^{2}[a]	80 ± 5	72 ± 12	NS	74 ± 3	72 ± 2	NS
Liver cyst(s) present on ultrasound %	0	3	NS	5	0	<0.05
History of inguinal hernia %	33	14	NS	7	5	NS
History of umbilical hernia %	20	6	NS	2	1	NS
Family history of intracranial aneurysm %	25	24	NS	22	36	NS
History of gross hematuria %	30	11	NS	39	6	<0.0001

[a] Age-adjusted mean ± SEM.

In adults, several risk factors for faster progression have been identified, including the *PKD1* gene, male gender, a younger age at diagnosis, the presence of hypertension, hematuria, and proteinuria, a younger age at onset of hypertension and hematuria, larger kidneys, and a younger age at incipient renal failure [7, 19–21]. However, disease progression and outcome have not been completely described in a large series of VEO-ADPKD patients. Because the disease begins in childhood, identifying risk factors and the disease course in the early years of life might provide the greatest potential for effective intervention in high-risk patients.

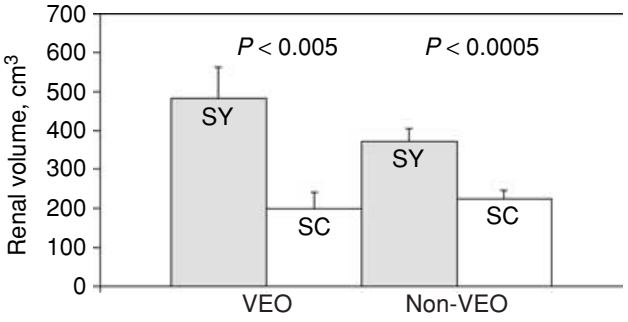

Fig. 3. At the last clinical research center visit, both VEO and non-VEO ADPKD children diagnosed due to signs or symptoms (SY) had larger (age-adjusted) renal volumes than ADPKD children diagnosed due to screening (SC).

The VEO-ADPKD patients had larger kidney size and a greater frequency of hypertension than non-VEO ADPKD children. This relationship between larger kidneys and more hypertension has been associated with the up-regulation of the intrarenal renin-angiotensin-aldosterone system (RAAS). Renin has been found to be overexpressed in polycystic kidneys [22]. It has been observed in high concentrations in cyst fluid, and the cyst epithelia have the ability to synthesize renin [23]. These observations with renal renin could lead to excess angiotensin II production in children with larger kidneys and more cysts, thus contributing to higher blood pressures. Moreover, angiotensin II is a growth factor for renal tubular cells and enhances the mitogenic actions of epidermal growth factor (EGF); thus, angiotensin II may contribute to a faster renal growth rate in hypertensive children with enlarged kidneys [24].

Renal enlargement is a marker for disease progression and renal volume may be a useful marker for disease progression in early stages of ADPKD when GFR is preserved [25]. In this regard, structural progression in terms of increased cyst numbers and kidney size was shown to be greater in VEO patients compared to non-VEO children, and in children who were diagnosed due to symptoms compared with children diagnosed due to screening. Because many of the children had too many cysts to count, it was necessary to use renal volume rather than cyst number for comparisons.

Both VEO and non-VEO ADPKD children with proteinuria had larger renal volumes than those without proteinuria. This finding is similar to that observed in adults with ADPKD. In adults, increased proteinuria is associated with faster progression of renal disease [21], and the present results in ADPKD children are also compatible with this interpretation.

Gross hematuria has been described as a risk factor for faster progression in ADPKD adults [26]. Hematuria is not common in children with ADPKD (15%) but in the present study both VEO and non-VEO ADPKD children with a history of hematuria had larger kidneys. Thus, hematuria may be associated with increased rate of progression in both children and adults. Renal stones as a cause of hematuria are very rare in ADPKD children [26].

To further assess the outcome and progression of ADPKD in childhood, the same risk factors were compared between ADPKD children who were diagnosed due to symptoms with those who were diagnosed for screening. The results demonstrate that both VEO and non-VEO ADPKD children diagnosed due to symptoms had decreased renal function as measured by serum creatinine, creatinine clearance, and estimated GFR. Renal volumes were also greater in children diagnosed due to symptoms. This was true even though some of the symptoms may not have been specifically related to ADPKD (such as urinary tract infection, which was a reason for diagnosis in 6 non-VEO children, all girls). At last follow-up, two VEO children who had been diagnosed due to symptoms (abdominal mass) had reached ESRD and none of the non-VEO had ESRD.

In the present study of infants and children with ADPKD the outcomes were better than in most previous reports. MacDermot et al analyzed ADPKD studies of 83 case reports presenting in utero or in the first few months of life. The reported mortality was 43% (36/83) in the first year of life [27]. This difference in outcomes from the current report may be related to a bias for VEO children with more severe disease to be published in case report studies. In the present study the children were all seen at the clinical research center, which may present a bias against more severely affected children. However, when the pedigrees were searched for affected children not studied here, there were no additional VEO children born between 1975 and 1997 who had reached ESRD. One VEO child born before 1975 reached ESRD at age 17; this child's family has been described in several other reports [28–30].

CONCLUSION

VEO children have worse age-adjusted renal function, larger renal volumes, more hypertension, and increased left ventricular mass index compared with non-VEO children. Proteinuria, hematuria, and signs/symptoms at diagnosis are associated with larger age-adjusted renal volumes in both VEO and non-VEO children. Over 90% of VEO children maintained preserved renal function well into childhood. Because larger kidneys are associated with increased morbidity and more rapid progression to ESRD, the potential for reducing renal growth and left ventricular mass by blockade of the RAAS and reduction in blood pressure level should be studied as a potential therapeutic goal starting in childhood [24]. Such a prospective, randomized study in ADPKD children

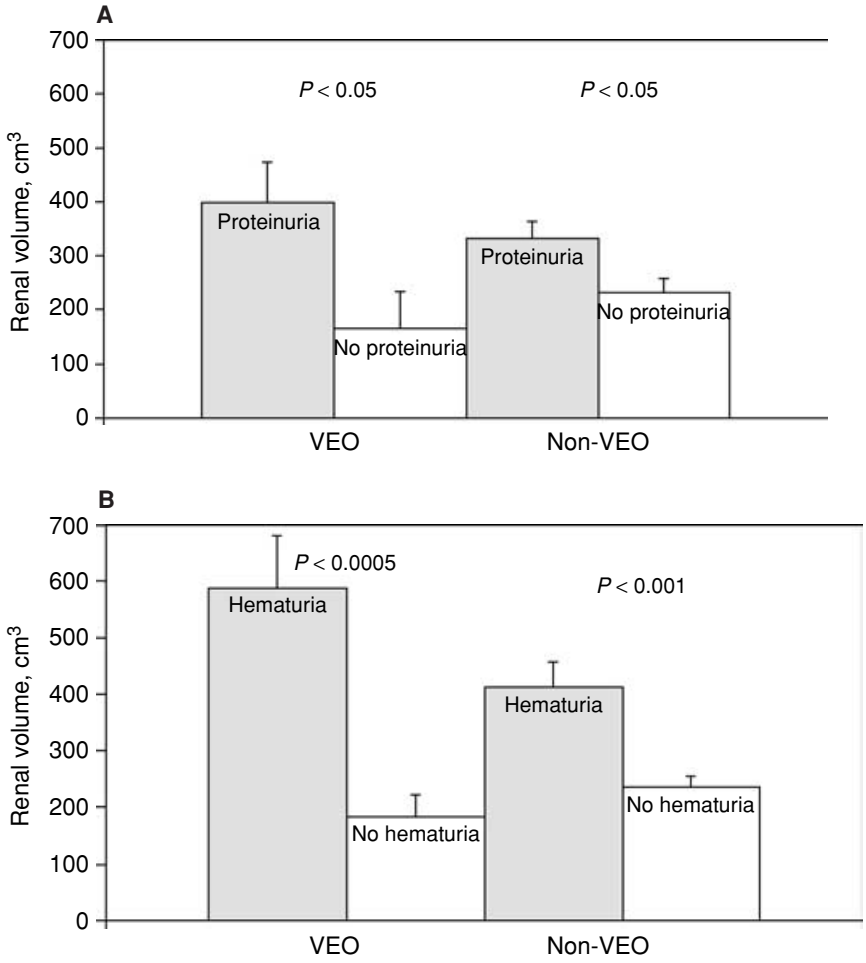

Fig. 4. Both VEO and non-VEO ADPKD children with (*A*) proteinuria or (*B*) hematuria had larger (age-adjusted) renal volumes than ADPKD children without these manifestations at the last clinical research center visit.

is underway at the UCHSC. Moreover, in counseling parents of a VEO child, the present results suggest that the physician can indicate the likelihood that reasonable kidney function will be maintained during childhood and adolescence. However, these children should be frequently monitored for complications such as hypertension and renal insufficiency.

ACKNOWLEDGMENTS

This research was supported by grant P01 DK34039 awarded by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; grants MO1 RR00051 and M01 RR00069 from the General Clinical Research Centers Program of the National Center for Research Resources, National Institutes of Health; and the Zell Family Foundation.

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