The Spectrum of Autosomal Dominant Polycystic Kidney Disease in Children[1]

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ABSTRACT

The natural history of autosomal dominant polycystic kidney disease (ADPKD) has not been well described in children, and it is not known whether a relationship exists between renal structural abnormalities and function in children as has been seen in adults. Therefore, 140 children from 67 ADPKD families were studied in a prospective study. Only 22 children came with a previous diagnosis of ADPKD. In 44% of all children, at least one cyst was found on ultrasound at a mean age of 8.7 yr. Of these, 60% were classified as having moderate disease on the basis of a total cyst number of 1 to 10 cysts, whereas 40% were considered to have severe disease with a total of more than 10 cysts. There was a significant relationship between the severity of the renal structural involvement and the frequency of flank and back pain, hypertension, and impaired renal concentrating capacity. However, GFR were not reduced in children with ADPKD and did not relate to structural severity. Thirty-nine children were seen for a follow-up visit 2 to 5 yr after the initial visit. No child had progressed from nonaffected to affected with ADPKD, but three of four children with only one cyst at the time of the initial study had progressed to bilateral cysts. Among the 22 ADPKD children who had a follow-up study, there was progression of the disease, reflected by an increase in cyst number and an increase in the frequency of pain and hypertension. However, GFR remained stable in all children. These observations begin to define the natural history of this disease in children, which is the necessary basis for designing future intervention studies.

Key Words: *Renal ultrasonography, genetics, hypertension, renal concentrating capacity, GFR*

Autosomal dominant polycystic kidney disease (ADPKD) for many years was dubbed adult polycystic disease, reflecting the belief that the disease did not occur in childhood. However, in the last 30 yr, reports have appeared describing ADPKD in childhood or even *in utero* (for a review, see reference 1). Most of the previously reported children came to the attention of physicians because they were symptomatic and thus represented the most severe end of the spectrum of childhood ADPKD. Moreover, those reports that reviewed asymptomatic children included small numbers of children, concentrated on limited aspects of the disease, did not relate structure to function, contained no controls, and had limited long-term follow-up information (2–5). Modern imaging techniques, particularly ultrasonography, appear to identify 60 to 90% of gene carriers under the age of 20 yr (4,6), thus enabling the early identification of asymptomatic children and ascertainment of the true spectrum of the disease in childhood. Therefore, we studied a large population of at-risk children in order to assess the utility of ultrasonography, to determine the signs and symptoms of the disease in children, to describe the renal functional abnormalities, and to begin to evaluate the natural history of the disease in children.

METHODS

Fifty-one adult individuals with ADPKD who had previously participated in an ongoing study of polycystic kidney disease at the University of Colorado Health Sciences Center were asked to have their children participate. Forty-seven of the parents agreed. In addition, 22 children from 18 families who were referred to us with a known diagnosis of ADPKD for further evaluation were also included in the study group, along with 11 siblings, most of whom had not been previously studied. The diagnosis of ADPKD in the parent was based on the finding of five or more

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cysts in both kidneys on ultrasound. All children and their affected parent were admitted for 2 days either to the General Clinical Research Center at the University of Colorado (51 children) or to the Pediatric Clinical Research Center at The Children's Hospital (89 children) between June 1985 and December 1992. They had a detailed history taken by a formalized interview with the parent and/or the child if he or she was old enough to provide independent information. Clinical assessment included questioning regarding the occurrence of abdominal, flank, or back pain or headaches. If the answer was yes, the frequency was noted. Urinary frequency was noted if the children (or their parents) said that they had to pass their urine more often than other children of the same age.

A complete physical examination was performed. All children underwent an abdominal ultrasound examination with a high-resolution real-time scanner (Acuson 1.28 EXP [Acuson, Mountainview, CA] with a 3.5- or 5-mHz transducer), and renal length, width and anteroposterior diameter were measured. Renal volume was then calculated with the formula for a modified ellipse: $4/3\ \pi$ (length/2) (anteroposterior diameter/4 + width/4)^2. Mean renal volume was calculated as the mean of both kidneys for each child. Cyst numbers and sizes were determined during real-time examination. A child was considered to have ADPKD if any renal cyst was found on ultrasound (4). If more than 15 cysts were present in one kidney, the exact number was not counted and the kidney was classified as having more than 15 cysts.

All children had multiple blood pressures measured during their stay (mean, 12 times). The measurements were done with the child in the sitting position with an automatic device (Dinamap; Critikon, Inc., Tampa, FL) and a cuff adjusted for the arm size of the child. Hypertension was defined as 50% or more of systolic and/or diastolic in-house blood pressure measurements being higher than the 95th percentile for age- and gender-matched children (7). Children with previously diagnosed hypertension who were on antihypertensive medications at the time of the study were also considered hypertensive.

All children had blood obtained for routine serum biochemistries. Laboratory analyses were performed by the Clinical Research Laboratories of the University Hospital and of The Children's Hospital. GFR was calculated from serum creatinine values and body length corresponding to the formula provided by Schwartz *et al.*: GFR = kL/Pcr with k = 0.45 for children younger than 2 yr old, k = 0.55 for children 2 to 12 yr old and for girls between 13 and 18 yr, and k = 0.70 for boys between 13 and 18 yr; L = length in centimeters; and Pcr = serum creatinine concentration in milligrams per deciliter (8). Hyperfiltration was defined as calculated GFR > 150 mL/min per 1.73 m^2. Urinary concentrating capacity was determined in 81 children who were older than 6 yr by measuring urinary osmolality after a 12-h overnight fast.

Thirty-nine children were seen for a follow-up visit for similar studies 2 to 5 yr (mean, 3.7 yr) after the initial visit. Blood pressures were taken in the same way at both visits.

Standard statistical techniques were used for all analyses. Continuous variables were compared between groups by use of the *t* test. Continuous variables are reported as the mean ± one standard error. Dichotomous variables were compared by the use of χ^2 analysis or, if cell sizes were small, Fisher's exact test. Significance was defined as $P < 0.05$. Significant *P* values are reported in the Text.

RESULTS

One hundred forty children at 50% risk for ADPKD from 67 families were studied. In 65 families, all of the children (< 18 yr) were studied. Family sizes ranged from one to six children, with 36% of the families with one child, 39% with two children, 15% with three, and 10% with four or more children.

In 118 children, the study was prompted only by their parent's participation in the project. Twenty-two children had a previous diagnosis of ADPKD. Of these, eight children had been evaluated only because of a positive family history. In three children, the diagnosis had been made after the incidental finding of enlarged, hyperechoic kidneys on a prenatal ultrasound. In four children, renal cysts had been found on ultrasounds done for reasons other than ADPKD; one child was screened because of prematurity, one child was evaluated for possible Marfan's syndrome, one child had a computed tomographic scan because of bilateral ureteric reflux, and one child without a previous family history of ADPKD had a gastrointestinal work-up for severe abdominal pain. Polycystic kidneys were found in this child as well as in her subsequently screened father. Only seven of these children had been evaluated because of symptoms suggestive of ADPKD, such as hematuria (two children), frequency (two children), abdominal mass (one child), urinary tract infection (one child), and hypertension (one child). The mean age at the time of diagnosis of these 22 children was 6 yr, whereas the other 40 children were diagnosed at a mean age of 10 yr. The mean age at the time of diagnosis of all 62 ADPKD children was 8.7 yr.

In the study population, there were 64 boys and 76 girls. The mean age of all children was 11 yr (range, 5 mo to 18 yr) at the time of their most recent study visit. The affected parent was the mother in 38 families (with 82 children) and the father in 29 families (with 58 children).

Ultrasonographic Findings

In 78 children (56%), no cysts were found on ultrasound (NADPKD), whereas 62 children had one or more cysts. This group was further divided on the basis of the severity of the renal involvement. Thirty-seven children (26%) were considered to have moderate disease (MADPKD), with a total of 1 to 10 cysts in both kidneys, and 25 (18%) were considered to have severe disease (SADPKD), with more than 10 cysts. The gender distribution was not significantly different between the three groups. SADPKD children were significantly older (mean age, 13 ± 1 yr) than MADPKD (mean age, 10 ± 1 yr; $P < 0.01$) and NADPKD (mean age, 10 ± 1 yr; $P < 0.05$) children. Renal volumes were not different between NADPKD and MADPKD children (mean renal volume, 92 ± 6 versus 103 ± 7 cm^3; P = not significant), but SADPKD children had significantly enlarged kidneys (mean renal volume, 210 ± 23 cm^3; $P < 0.0001$ versus both NADPKD and MADPKD). This difference was still significant after adjusting for age, height, and body surface area; the adjusted mean renal volumes were 190, 110, and 96 cm^3 for SADPKD, MADPKD, and NADPKD children, respectively.

Eleven children had only unilateral involvement with four cysts or fewer. The mean age of the children with unilateral involvement was 9 ± 1 yr, significantly younger than children with bilateral cysts (12 ± 1 yr; $P < 0.05$). Six children had a single renal cyst. One boy in the SADPKD group had a single liver cyst at the age of 16 yr; no other child had liver cysts on ultrasound.

Of the 22 children with a previous diagnosis, 13 were SADPKD (59%) compared with 30% of the 40 children first diagnosed at our center ($P < 0.05$). The mean age of these 22 children was not higher than the mean age of the other 40 children.

Symptoms

The most common symptom related to the renal disease was flank or back pain (Table 1). Significantly more SADPKD children complained of flank pain or back pain than MADPKD or NADPKD children. One SADPKD child and four MADPKD children complained of abdominal pain, whereas only one NADPKD child had abdominal pain ($P < 0.05$, MADPKD versus NADPKD). Nausea tended to be more common in SADPKD children than in MADPKD and NADPKD children, but the difference was not statistically significant. Neither the prevalence nor frequency of headaches was significantly different between the groups. Two SADPKD children had palpitations compared with none of the MADPKD and NADPKD children ($P < 0.05$).

Frequency was reported by 36% of the SADPKD children as compared with 16% of the MADPKD and 8% of the NADPKD children ($P < 0.05$, SADPKD versus NADPKD). The prevalence of nocturia was not significantly different between the three groups. A history of previous urinary tract infection or of hematuria was obtained with similar frequency in the three groups (Table 1).

TABLE 1. Symptoms in the three groups of children (%)[a]

	SADPKD ($N = 25$)	MADPKD ($N = 37$)	NADPKD ($N = 78$)
Flank Pain	28[b]	0	5
Back Pain	32[b]	5	4
Abdominal Pain	4	11[c]	1
Nausea	8	3	0
Headaches	36	22	20
Palpitations	8[d]	0	0
Frequency	36[d]	16	8
Nocturia	17	19	12
Hx of UTI	20	11	15
Hx of Hematuria	8	11	4
Surgery for IH	16[d]	5	1

[a] Hx, history; UTI, urinary tract infection; IH, inguinal hernias.
[b] $P < 0.05$, SADPKD versus both MADPKD and NADPKD.
[c] $P < 0.05$, MADPKD versus NADPKD.
[d] $P < 0.05$, SADPKD versus NADPKD.

Four children in the SADPKD group had surgery for inguinal hernias, which were bilateral in two children. Two of the MADPKD children and only one NADPKD child had a history of inguinal hernia repair ($P < 0.05$, SADPKD versus NADPKD).

Six children (24%) of the SADPKD group came to the study with a previous diagnosis of hypertension, and four of them were on antihypertensive medication at the time of their study visit. Only one child (3%) of the MADPKD group had a prior diagnosis of hypertension ($P < 0.05$ versus SADPKD), but she was not being treated with medications at the time of the study. None of the NADPKD children had a prior diagnosis of hypertension ($P < 0.05$ versus SADPKD).

Fifty-seven percent of the NADPKD children and 49% of the MADPKD children did not report any of these symptoms, whereas only 12% of the SADPKD children had no symptoms ($P < 0.01$, SADPKD versus both MADPKD and NADPKD).

Findings on Physical Examination

When comparing heights and weights of all children in the three groups with published percentiles for age and gender, there was no difference in the number of children being below the 5th or 50th percentile between the three groups, nor was the distribution of the children within percentile categories different between the three groups. Palpable

kidneys were found in six of the SADPKD children (24%), as compared with two of the MADPKD children (5%) and one NADPKD child (1%) ($P < 0.05$, SADPKD versus both MADPKD and NADPKD).

Excluding three SADPKD children on antihypertensive medication whose blood pressures were not elevated at the study visit, 17% of the SADPKD children had systolic hypertension compared with 5% of the MADPKD children and 3% of the NADPKD children ($P < 0.01$, SADPKD versus NADPKD). Diastolic hypertension was noted in 18% of the SADPKD children, in none of the MADPKD children, and in one NADPKD child (1%) ($P < 0.01$, SADPKD versus both MADPKD and NADPKD). Both systolic hypertension and diastolic hypertension were observed in two SADPKD children (9%) and in none of the MADPKD and NADPKD children ($P < 0.01$, SADPKD versus NADPKD). When considering the three children on antihypertensive medication as having both systolic and diastolic hypertension, 20% of the SADPKD children were hypertensive.

Renal Function Studies

Serum creatinine values were not significantly different between the three groups (0.9 mg/dL SADPKD versus 0.7 mg/dL both MADPKD and NADPKD; P = not significant). However, GFR as calculated by the formula of Schwartz *et al.* were significantly higher in the SADPKD children (123 ± 7 mL/min per 1.73 m^2) than in the NADPKD children (112 ± 4 mL/min per 1.73 m^2; $P < 0.05$); the MADPKD children had glomerular filtration values in between and not significantly different from those of the SADPKD or NADPKD children (116 ± 5 mL/min per 1.73 m^2). Sixteen percent of the SADPKD children had hyperfiltration (calculated GFR > 150 mL/min per 1.73 m^2), which was not significantly different from 8% of the children in the MADPKD group and 11% of the children in the NADPKD group. None of the children with hyperfiltration were hypertensive.

Maximum urinary osmolality after a 12-h overnight fast was determined in 11 SADPKD children, in 24 MADPKD children, and in 45 NADPKD children. It was significantly reduced in SADPKD children (823 ± 54 mosm/kg) as compared with MADPKD children (940 ± 22 mosm/kg; $P < 0.05$) and NADPKD children (945 ± 21 mosm/kg; $P < 0.05$).

Follow-Up Studies

Thirty-nine children had a follow-up visit; of these, 22 had been classified as ADPKD on their first visit and 17 as NADPKD. No child was reclassified between these two groups after the second visit. However, the severity of disease did change. Fourteen of the 22 ADPKD children had 1 to 10 cysts (MADPKD) on the first study visit, and three of them progressed to more than 10 cysts (SADPKD) on the follow-up visit. Four children had only one cyst at the initial ultrasound study; three of them progressed to bilateral cysts, totaling three in two children and four in one child, at the follow-up study after a mean of 4 yr. Overall, 13 children had an increase in cyst numbers between the two study visits, with a mean increase of 5.3 cysts in the 11 children in whom exact cyst numbers from both visits were available. There were three children who already had more than 15 cysts on their first study visit, one child who progressed from a total of 12 cysts to more than 15 cysts per kidney, and one child with progression from 6 to 15 cysts to more than 15 cysts in each kidney. Three children had fewer cysts at the time of the second study. However, in two of them, body habitus made ultrasonography technically difficult. The mean diameter of the largest cyst of all ADPKD children increased by 0.16 ± 0.6 cm/yr, from 1.9 to 2.5 cm over the follow-up period.

Renal volumes increased in both NADPKD and ADPKD children as the children grew between the two study visits; the increase in renal volume tended to be greater in the ADPKD children (13 ± 3 cm^3/yr) than in the NADPKD children (6 ± 1 cm^3/yr; P = 0.06).

Among the 22 affected children who had a follow-up visit, flank or back pain increased from 10 to 19%, and the number of children without any symptoms decreased from 30 to 25%. In addition, two had newly developed systolic hypertension on the second study visit, whereas none of the NADPKD children had either systolic or diastolic hypertension develop.

Serum creatinine concentrations had increased slightly in both ADPKD and NADPKD children at the follow-up study as they grew older. There was no difference in GFR in either group between the first and second study.

DISCUSSION

Although there are now many reports describing ADPKD in childhood and even *in utero*, there has been no comprehensive study of a large number of in at-risk children. Therefore, many aspects of ADPKD children have not been well defined. We particularly wished to define the utility of ultrasonography, the structural and functional relationship that had not been previously addressed in children, and the natural history of the disease. Ultrasonography was shown in this large group of children to be a valuable diagnostic tool. By the criterion of any renal cyst in a child of an ADPKD family, ADPKD was diagnosed in 62 children (44%). Because we examined entire families, one would expect 50% of the children to be affected. Although gene-linkage results are not yet available for all of our children, this high rate of positive diagnosis is similar to the findings in

a recent study by Bear *et al.*, who reported a rate of false-negative ultrasonographic diagnosis of 8% in 10- to 19-yr-old offspring of ADPKD1 families; this rate was estimated from Mendelian expectation and confirmed by linkage analysis in 10 ADPKD1 families (6). In this regard, only two children in our study came from the one large family known to be of the ADPKD2 genotype. They were 4 and 11 yr old and did not have detectable renal cysts. The ultimate assessment of the accuracy of ultrasonography in diagnosing ADPKD in children will only be possible when the gene status of ADPKD1 and ADPKD2 children can be determined by direct genetic analysis.

In adults, a relationship between structure and function has been demonstrated. Patients with larger cysts and renal volumes are more likely to have pain (9–11) and gross hematuria (12) than are patients with smaller kidneys. Moreover, there is an inverse relationship between maximal urinary osmolality and renal volume (13). Renal volume also has a relationship with renal function, independent of age, with patients with large kidneys having worse renal function (14). Hypertensive patients with normal renal function have significantly larger renal volumes than do age-matched normotensive ADPKD patients (15). These observations suggest a pathogenetic role of the renal cystic process in the development of symptoms and functional abnormalities.

For the assessment of the severity of the renal cystic process and correlation with functional abnormalities, we arbitrarily grouped the children by the criterion of whether they had a total of 1 to 10 or more than 10 cysts in both kidneys. Thus, 25 children (40% of the affected children) were classified as having severe disease, and 37 were classified as having moderate disease. The children with severe disease were significantly older than the children with moderate disease, suggesting disease progression with age. The gender distribution was not different between the groups, which may suggest that the rate of disease progression does not differ between genders at this early stage, whereas in adults, renal disease progression seems to be faster in men than in women (14,16).

As in the adult studies, we found a relationship between the severity of the renal structural involvement and flank and back pain, hypertension, and renal concentrating capacity in these ADPKD children. Flank and back pain were reported significantly more often by children with severe disease than by children with moderate or no disease. Only 60% of SADPKD children were without flank or back pain compared with 94% of the MADPKD children and 92% of the NADPKD children.

The prevalence of hypertension and its relationship to renal structure were also studied. Significantly more children of the SADPKD group came with a previous diagnosis of hypertension than children of the MADPKD group (24 versus 3%) or the unaffected children (0%). All children on antihypertensive medication at the time of the study were in the SADPKD group. Moreover, significantly more SADPKD children were diagnosed with systolic, diastolic, or both systolic and diastolic hypertension than NADPKD children.

The relationship between the severity of the renal structural involvement and the prevalence of hypertension suggests that intrarenal structural abnormalities play a role in the pathogenesis of hypertension. In ADPKD adults, it has been shown that the renin-angiotensin-aldosterone system is activated in hypertensive patients with normal renal function, possibly because of intrarenal ischemia caused by the compression of the arterioles by cysts (17,18). Whether the renin-angiotensin system is also activated as a mediator of hypertension in childhood has not yet been examined.

Hypertension has been noted to occur frequently in previous reports on ADPKD children. In a study by Parfrey *et al.*, 33% of ADPKD children between 10 and 19 yr had blood pressures more than 2 SD above the mean for age and gender in the general population (19). In another study, young ADPKD adults between 15 and 25 yr of age with normal renal function had significantly higher mean arterial blood pressure on 24-h ambulatory monitoring than did controls, both during daytime and nighttime (20). Moreover, the median left ventricular mass index was significantly higher in these young ADPKD individuals than in the controls. This attests to the biologic significance of the blood pressure elevation in these children.

We also found a relationship between the renal structural derangement and the decrease in urine concentrating capacity. Only the SADPKD children had significantly reduced urinary osmolality after water deprivation. The mechanism for the early decrease in concentrating capacity is not entirely clear. However, disruption of the renal medulla by cysts is likely involved. In addition, vasopressin resistance of medullary collecting ducts has been shown in a drug-induced animal model (21) and in human ADPKD cells in tissue culture (22).

Interestingly, the relationship between structure and function, as shown for tubule function by the reduced concentrating capacity, was not seen with glomerular function. There were no differences between the three groups in serum creatinine concentrations, and GFR as calculated by the Schwartz formula were higher in SADPKD than in NADPKD children. It is important to note that only one child in this study had a serum creatinine concentration above the range obtained for NADPKD children. This boy had been diagnosed with hypertension and enlarged kidneys at birth and progressed to ESRD at the age of 4 yr. None of the children who were diag-

nosed by our screening study had renal insufficiency.

This is in contrast to other studies that reported more severely affected children (3–5). This worse outcome in the previous studies resulted from the inclusion of affected children identified by retrospective reviews of hospital and autopsy records, and most of the children had been evaluated for symptoms (3,5). Moreover, many of these previously reported children were diagnosed in their first year of life, and this subgroup of patients appears to have a worse outcome than children diagnosed later in life (1,3–5). Despite the better outcome in our study, selection of more severely affected patients occurred to some extent as well. This study included eight children with a previous diagnosis of ADPKD because of symptoms and nine children who had been diagnosed in their first year of life who have been previously reported by us (1). Even when excluding the children diagnosed in their first year of life, the children who came to our study with a previous diagnosis had more severe disease in terms of cyst number than did the children first diagnosed by this study. In spite of this, all children except one with a diagnosis at birth had a good outcome with regard to renal function.

Of the extrarenal manifestations, inguinal hernias requiring surgery occurred significantly more often in ADPKD than in NADPKD children. This has also been observed in previous studies (23,24). Only a single liver cyst was found in one 16-yr-old boy, which confirms previous reports on the rarity of hepatic cysts in children (25–27).

Thirty-nine children had a second study at a mean interval of 3.7 yr after their first. None of the 17 children originally classified as NADPKD (mean age, 6.9 ± 1.0 yr) had developed cysts by the time of the second study visit (mean age, 10.4 ± 1.1 yr). Among the 22 children diagnosed with ADPKD at the first study visit, there was disease progression in terms of cyst number, cyst size, and increase in renal volume in 19 children. There was no difference in calculated GFR corrected for body surface area between the first and the second study in any of the ADPKD children. This also supports the idea that renal insufficiency will not develop rapidly in most ADPKD children. Longer follow-up periods are necessary to assess factors associated with decreasing renal function in children.

As we have shown here, the diagnosis of ADPKD is often possible in childhood. Therefore, the question arises as to whether at-risk children should be screened outside a research setting. In this regard, the guidelines of the National Kidney Foundation Workshop on gene testing in ADPKD should be followed because ultrasonography also can provide presymptomatic diagnosis (28). Children with clinical signs and symptoms suggestive of ADPKD should undergo an ultrasound evaluation in order to optimize treatment. Completely asymptomatic at-risk children should have their blood pressure monitored twice per year, and if hypertension is found by the use of age- and gender-specific data (7), then a diagnosis should be sought because it influences treatment decisions. Some consideration should be given to obtaining ultrasonography prior to having a child engage in contact sports such as football because repetitive episodes of gross hematuria appear to influence renal outcome (12). Additionally, many parents wish to know the status of their children. Before any diagnostic test for ADPKD in a child, the parents and, if appropriate, children must be counseled about the implications for health care and insurability.

In summary, in this study, we have shown that ultrasonography is a valuable diagnostic tool in ADPKD children and that a relationship exists between structural and functional abnormalities, suggesting a pathogenetic role of cysts in the development of signs and symptoms. During short-term follow-up (2 to 5 yr) of 22 children, we found renal structural disease progression in 19, but GFR remained normal in all. These observations provide important counseling information for physicians caring for these children, and they enable investigators to develop criteria upon which to base future intervention studies.

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