Cardiovascular Abnormalities in Children With Autosomal Dominant Polycystic Kidney Disease[1]

D. Dunbar Ivy, MD,[2] Elizabeth M. Shaffer, Ann M. Johnson, William J. Kimberling, Asya Dobin, and Patricia A. Gabow

D.D. Ivy, E.M. Shaffer, The Children's Hospital, Denver, CO
D.D. Ivy, E.M. Shaffer, A.M. Johnson, P.A. Gabow, The University of Colorado Health Sciences Center, Denver, CO
W.J. Kimberling, A. Dobin, Boy's Town National Research Institute, Omaha, NE
P.A. Gabow, Denver Health and Hospitals, Denver, CO

(J. Am. Soc. Nephrol. 1995; 5:2032–2036)

ABSTRACT

It is known that adults with autosomal dominant polycystic kidney disease (ADPKD) have an increased incidence of cardiovascular abnormalities, including mitral valve prolapse. The cardiac manifestations of ADPKD in the pediatric population have not been well established. To determine the cardiac manifestations of children with ADPKD, echocardiography was performed in 154 children of 66 families in which one parent has ADPKD. Eighty-six affected children and 68 unaffected children were evaluated in a prospective, single-blinded manner by echocardiography. Affected children were defined as those with any cysts on a concurrent renal ultrasound or those predicted to be gene carriers by gene linkage analysis. A 12% incidence of mitral valve prolapse was found in the affected children compared with only 3% of the unaffected children ($P < 0.05$). ADPKD children, but not their unaffected siblings, demonstrate a significant correlation between left ventricular mass index and systolic blood pressure. Moreover, hypertensive ADPKD children have significantly larger left ventricular mass index than do normotensive ADPKD children. A 3.5% incidence of congenital heart disease was found in the affected group, whereas 2.9% of the unaffected children had congenital heart disease. It was concluded that systemic manifestations of ADPKD, particularly cardiovascular abnormalities, are present even in childhood and these warrant the clinician's attention.

Key Words: *Autosomal dominant polycystic kidney disease, mitral valve prolapse, congenital heart disease, left ventricular mass index, echocardiography*

Autosomal dominant polycystic kidney disease (ADPKD) has been shown to be a systemic disorder in adults (1). One of the most common extrarenal manifestations is cardiac valve abnormalities (2,3), with mitral valve prolapse (MVP) occurring in about 26% of affected adults compared with 2% of control subjects (2–4). Mitral regurgitation, aortic insufficiency, myxomatous degeneration of the mitral valve, and the need for surgical valve replacement have also been documented in adults with ADPKD (2–4). In addition to the valvular abnormalities, hypertension and its consequent left ventricular hypertrophy are common in affected adults. Moreover, higher blood pressures and larger left ventricular mass indices (LVMI) are evident even in young adults with ADPKD compared with unaffected controls (5). Although it is clear that ADPKD is often manifested in childhood (6–8), there is little information regarding the extrarenal manifestations of ADPKD in this age group. Therefore, to determine the cardiac manifestations of ADPKD in children, we studied the children of adults with ADPKD who were ongoing participants in the longitudinal study of ADPKD at the University of Colorado Health Sciences Center.

METHODS

Between June 1991 and September 1994, all adults with ADPKD who had participated in our ongoing study of ADPKD were asked to enroll their minor children in the study. All children were admitted to the Pediatric Clinical Research Center at the University of Colorado/The Children's Hospital. Written informed consent was obtained. Each child underwent a renal ultrasound. If any renal cysts were present, the child was considered affected (8). If gene linkage analysis (described below) yielded a high probability that a child was a gene carrier, that child was also considered affected. If no renal cysts were detected on ultrasound and gene linkage analysis yielded a high probability that a child was not a gene carrier or was not informative, the child was considered unaffected.

All subjects had multiple ambulatory blood pressures obtained while they were at the Clinical Research Center (mean, 11 times). Measurements were obtained with a programmable blood pressure monitor (Dinamap 1846 SX (Critikon, Tampa, FL)) and an appropriately sized blood pressure cuff. Children were classified as hypertensive if more than 50% of either systolic or diastolic blood pressures were greater than the 95th percentile for age- and gender-matched children (9). Children with previously diagnosed hypertension who were on antihypertensive medications at the time of the study were also considered hypertensive.

[1] Received December 12, 1994. Accepted March 7, 1995.

[2] Correspondence to Dr. D. Ivy, Section of Pediatric Cardiology, Box B100, The Children's Hospital, 1056 East 19th Ave., Denver, CO 80218.

1046-6673/0512-2032$03.00/0
Journal of the American Society of Nephrology

Routine echocardiography was evaluated by a pediatric cardiologist without knowledge of ADPKD status. Standard two-dimensional and Doppler echocardiograms were performed with the patients supine by the use of an Accuson 128XP/5 ultrasound machine (Mountain View, CA). From the real-time M-mode echocardiogram, the left ventricular internal diameter in diastole (LVDD), the left ventricular internal diameter in systole (LVSD), the posterior wall thickness in diastole (PWT), and the ventricular septal thickness in diastole (IVS) were measured in the parasternal short axis view. Left ventricular ejection time was measured from the aortic valve M-mode and was corrected for heart rate by dividing it by the square root of the RR interval. Left ventricular mass (LVM) was determined by the formula LVM = $0.80\{1.04 \times (LVDD + PWT + IVS)^3 - (LVDD)^3\} + 0.6$ (10). Normal values for LVM and LVMI have been previously reported (11). Mitral inflow patterns, including the total velocity time integral of the E wave and A wave, the velocity time integral of the E wave and the A wave, the E to A ratio, the peak E wave velocity, and the peak A wave velocity, were measured by the use of standard techniques (12).

MVP was diagnosed echocardiographically when there was >2 mm posterior systolic displacement of the mitral valve in two views or more by two-dimensional echocardiography. Mitral regurgitation by Doppler analysis was also noted.

Blood was obtained from all children for gene linkage analysis. Genomic DNA was prepared from peripheral blood lymphocytes on an Applied Biosystems 340A nucleic acid extractor (Foster City, CA) according to the manufacturer's protocol and stored at −80°C. Sense and antisense primers were made for chromosomes 16p and 4q microsatellite DNA polymorphisms with a Cruachem SP5250 DNA synthesizer (Sterling, VA). The specific markers, D16S291 and D16S283 (SM7), that flank the ADPKD1 gene were used to test for linkage with the 16p region on chromosome 16 and to detect presymptomatic gene carriers in families. Additional data for the 16p markers 3'HVR, D16S83 (EKD2), and D16S84 (CMM65) were also available for some families. Markers D4S231 and D4S414 were used to detect linkage to the ADPKD2 region on chromosome 4q.

Amplification of genomic DNA was done by the use of polymerase chain reaction, which was carried out on a Stratagene SCS-96 thermocycler (La Jolla, CA). Polymerase chain reaction was performed in a total volume of 25 μL containing the following: 40 ng of genomic DNA; 150 ng of each primer in a particular pair; 50 nM KCL; 10 mM Tris (pH 8.3); 1.5 mM $MgCl_2$; 0.2 mM dGTP, dCTP, and dTTP; 0.025 mM dHTP; 1 μCi of [$^{\alpha}P^{32}$]dATP (800 Ci/nmol); and 1 Taq unit of DNA polymerase (Perkin Elmer Cetus, Branchburg, NJ). DNA was denatured for 1 min at 94°C, annealed with primers at 55°C for 2 min, and extended with 0.5 U of Taq DNA polymerase at 72°C for 2 min, for a total of 32 cycles, followed by a final extension step at 72°C for 10 min. Actual conditions varied slightly for certain primers in order to optimize amplification. Fragments were separated on a 6% denaturing acrylamide gel, and the whole gel was autoradiographed for visualization of the bands. Bands were scored according to allele sizes.

Marker data were used to construct the haplotypes and predict diagnosis by linkage. An at-risk child having the haplotype transmitted with the disease was considered to be a carrier of the ADPKD gene.

Data are reported as the mean plus or minus the standard error. Frequencies were compared between groups by the use of χ^2 analysis. Continuous variables were compared by use of the *t* test or, when fewer than 20 in a group, with rank sum analysis. A *P* value less than 0.05 was considered significant; *P* values less than 0.10 are reported in the text.

RESULTS

The study included 154 children from 66 families ranging in age from 8 months to 17 yr. Seventy-nine children had one or more cysts detectable on ultrasound, and seven children with no cysts were predicted to be gene carriers by gene linkage analysis; these children were considered positive for ADPKD. Of the remaining 68 children without cysts, 24 were predicted by gene linkage analysis to not carry the ADPKD gene; the remaining 42 children had no gene linkage analysis prediction. Four children were in an ADPKD2 family; one was affected. Five children (three ADPKD, two unaffected) with known or newly diagnosed congenital heart disease (CHD) were excluded from analysis. The clinical characteristics of the remaining children are detailed in Table 1. There were no significant differences between the groups regarding age, gender distribution, body surface area, or heart rate. ADPKD children tended to have higher mean systolic blood pressures and were more likely to be classified as hypertensive.

MVP was detected by two-dimensional echocardiography in 10 (12%; 95% confidence interval, 5.9 to 21.0) of the affected children and 2 (3%; 95% confidence interval, 0.4 to 1.5) of the unaffected children ($P < 0.05$). One of the unaffected children with MVP was predicted to be unaffected by gene linkage; the other was in an uninformative family. No child in an ADPKD2 family had MVP. The ADPKD children with MVP were older than the ADPKD children without MVP (Table 2); all 10 children with MVP were older than 10 yr of age ($P < 0.01$). Also, a greater percentage of ADPKD children with MVP had more severe renal involvement (>10 cysts) than did ADPKD children without MVP (70 *versus* 30%; $P < 0.05$). Two of the ADPKD children with MVP were siblings. Eight of the affected parents of the 10 ADPKD children with MVP also underwent echocardiography as part of an independent study, and 5 (62%) of the 8 also had MVP,

TABLE 1. Subject data[a]

Parameter	Affected	Unaffected	*P* Value
N	83	66	
Male:Female	41:42	23:43	
% Female	51%	65%	NS
Age (yr)	9.6 ± 0.5	9.6 ± 0.5	NS
BSA (m^2)	1.15 ± 0.05	1.13 ± 0.05	NS
HR (BPM)	91 ± 2	91 ± 2	NS
SBP (mm Hg)	109 ± 1	105 ± 1	=0.06
DBP (mm Hg)	63 ± 1	62 ± 1	NS
HTN (*N*, %)	11 (13%)	0 (0%)	<0.05
MVP (*N*, %)	10 (12%)	2 (3%)	<0.05

[a] Values are mean ± SE. BSA, body surface area; HR, heart rate; BPM, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension.

TABLE 2. MVP in ADPKD children[a]

Parameter	+MVP	−MVP	*P* Value
N	10	73	
Male:Female	7:3	34:39	
% Female	30%	53%	NS
Age (yr)	14.0 ± 0.8	9.0 ± 0.5	<0.001
BSA (m^2)	1.50 ± 0.08	1.10 ± 0.05	<0.005
HR (BPM)	79 ± 4	93 ± 2	<0.005
SBP (mm Hg)	116 ± 3	108 ± 1	<0.05
DBP (mm Hg)	67 ± 2	63 ± 1	=0.06
LVMI (g/m^2)	86.5 ± 6.4	76.8 ± 1.8	=0.07

[a] Values are mean ± SE. +MVP, ADPKD children with MVP; −MVP, ADPKD children without MVP. See footnote to Table 1 for other abbreviations.

compared with 46% of the parents of ADPKD children without MVP (24 of 52 parents studied had MVP; not significant [NS]). One of the 10 ADPKD children with MVP had a past history of an acute neurologic event characterized by transient right focal numbness, visual loss, and loss of consciousness. Tricuspid valve prolapse was noted in three (4%) of the affected children and none of the unaffected children (NS).

There was no significant difference in LVMI between the two groups when considered as a whole (Table 3) or when separated by gender. However, when LVMI was compared with both systolic blood pressure and diastolic blood pressure in affected and unaffected children, there was a significant positive relationship between LVMI and systolic blood pressure ($R = 0.43$, $P < 0.0001$) in affected children but not in unaffected children (Figure 1). The 11 ADPKD children with hypertension had greater LVMI than did normotensive ADPKD children (87.1 ± 4.8 *versus* 76.6 ± 1.8 g/m^2; $P < 0.05$). After adjusting for age and gender, this relationship was still suggestive ($P = 0.08$). LVMI was not significantly different between normotensive ADPKD children and their normotensive unaffected siblings (76.6 ± 1.8 *versus* 73.0 ± 1.9; NS).

Four of the 10 ADPKD children with MVP and both of the unaffected children with MVP had mitral regurgitation diagnosed by Doppler echocardiography. There were no significant differences between the two groups regarding mitral inflow patterns or regurgitation of any valve.

TABLE 3. Echocardiographic data[a]

Parameter	Affected	Unaffected	*P* Value
Number	83	66	
LVDD (mm)	41.1 ± 0.8	39.9 ± 0.8	NS
LVSD (mm)	25.0 ± 0.5	24.1 ± 0.5	NS
IVS (mm)	6.6 ± 0.2	6.4 ± 0.2	NS
PWT (mm)	6.4 ± 0.2	6.1 ± 0.2	NS
LVMI (g/m^2)	78.0 ± 1.7	73.0 ± 1.9	=0.06
FS (%)	39 ± 1	40 ± 1	NS

[a] Values are mean ± SE. LVDD, left ventricular internal diameter in diastole; LVSD, left ventricular internal diameter in systole; IVS, ventricular septal thickness in diastole; PWT, posterior wall thickness in diastole; FS, fractional shortening.

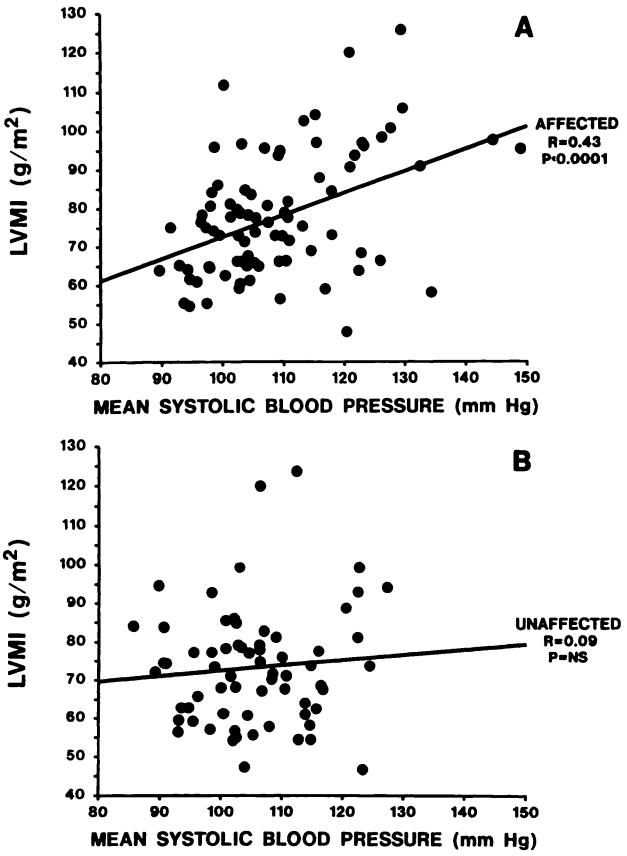

Figure 1. Mean systolic blood pressure measurements in 83 affected ADPKD children (A) and 66 unaffected children (B) were regressed against LVMI. In the affected children, systolic blood pressures correlated with LVMI ($R = 0.43$, $P < 0.0001$).

Three children with ADPKD were found to have CHD. The diagnoses of these children are atrial septal defect, patent ductus arteriosus, and congenital endocardial fibroelastosis. Two unaffected children had CHD, consisting of Ebstein's anomaly of the tricuspid valve and pulmonary stenosis. One of these children was predicted not to carry the ADPKD1 gene by linkage analysis, and the other was in a family uninformative for gene linkage.

DISCUSSION

Over the last decade, the understanding of ADPKD has expanded. We now know that this disease is manifested in children as well as adults and that the phenotypic manifestations of ADPKD include both renal and extrarenal manifestations (1,6–8). However, there is a paucity of information regarding the extrarenal manifestations in children. Because MVP is one of the most common manifestations in adults (2,3), we investigated the frequency of this abnormality in chil-

dren. The prevalence of MVP in the pediatric population ranges from 0.5 to 13% (13,14). The prevalence of MVP in children with ADPKD is unknown. We found that 12% of the ADPKD children compared with 3% of the unaffected children had MVP. This compares with the 26% frequency of MVP found in ADPKD adults and the 2% frequency found in adult control subjects in our previous study (2). Others have found similar frequencies (3). The fact that the ADPKD children with MVP were older than those without MVP suggests that this phenotypic manifestation may increase with age, as do both renal and hepatic cystic diseases. Also, the more severe renal structural involvement in the ADPKD children with MVP compared with those without MVP is compatible with these children having an overall more severe disease state.

The frequency of congenital cardiac defects in this population (3.5% in the ADPKD children and 2.9% in the unaffected children) was much greater than the estimated frequency of 0.8% found in the general population of children (15). There are limited data on the frequency of congenital cardiac diseases in adults with ADPKD, but Leier *et al.* noted a 36% occurrence of bicuspid aortic valve in ADPKD patients (4). A 6-yr-old child with ADPKD with severe renal structural involvement and an atrial septal aneurysm has been reported (16). Moreover, there is a frequent association of congenital cardiac abnormalities and other types of renal cystic disease (17). The occurrence of CHD and/or MVP in some unaffected children could be consistent with these children being gene carriers who have not yet developed renal cysts. This appears not to be the case in that one unaffected child with CHD and one unaffected child with MVP were not gene carriers; the other two unaffected children with abnormalities could not be given gene linkage predictions because their families were uninformative. It is also possible that there is another genetic factor that results in cardiac abnormalities in ADPKD because both Hossack *et al.* and Timio *et al.* have shown a higher prevalence of MVP in adult unaffected family members than in controls (2,3). The occurrence of MVP in two ADPKD siblings and in the affected parent of five of eight affected children with MVP raises the possibility that MVP clusters in families, as is seen in intracranial aneurysms in certain families with ADPKD (18).

In adults, left ventricular hypertrophy is the other major cardiac abnormality of ADPKD, reflecting at least in part the high incidence of systemic hypertension in adult ADPKD. Approximately 60% of adult ADPKD patients with normal renal function and 80% of patients with end stage renal disease have hypertension. A recent study demonstrated that approximately 30% of young adults with ADPKD are hypertensive and that young adults with ADPKD, but not children, have LVM that although in the normal range, were greater in patients than in controls (5). Our study demonstrates that children with ADPKD have higher LVM than do their unaffected siblings and that hypertensive ADPKD children have higher LVM than do normotensive ADPKD children. This has major long-term implications because increased LVMI has been demonstrated in adults to be an independent risk factor for major cardiac sequelae (19). In addition, LVMI had a significant direct relationship with systolic blood pressure in ADPKD children but not in unaffected children. The relationship between LVMI and systolic blood pressure was seen in the ADPKD children, even when subjects having mean systolic blood pressures greater than 120 mm Hg were removed from the analysis. This is consistent with the hypothesis that there may be a predilection for increased LVMI in ADPKD, even in the absence of hypertension (2,20).

These findings of MVP and increased LVMI in children with ADPKD suggest the systemic nature of the disease even early in its course. Moreover, this information suggests that physicians caring for children with ADPKD should perform careful cardiac histories and examinations and pursue abnormal findings.

ACKNOWLEDGMENTS

This research was supported by Grant 5 P01 DK34039, Human Polycystic Kidney Disease (PKD), awarded by the Department of Health and Human Services, Public Health Service, NIDDK; Grant M01 RR00069 from the General Clinical Research Centers Program, National Center for Research Resources, NIH; and The American Heart Association of Colorado (CF-035-93).

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