

Clinical Presentation and Outcome of Autosomal Dominant Polycystic Kidney Disease in Pakistan: A Single Center experience

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Abstract

Objective: To delineate clinical presentation and outcome of Autosomal Dominant Polycystic Kidney Disease (ADPKD) in terms of need for renal replacement therapy of kidney transplantation in Pakistani patients.

Methods: Patients with ADPKD were identified using strict clinical criteria. Medical charts were evaluated retrospectively for initial presenting complaints, co-morbidities, family history of ADPKD, any palpable mass on abdominal examination, cardiac examination for any abnormal finding and use of any anti-hypertensive drugs. Laboratory parameters were assessed. Chi square and Logistic regression analyses at 95% CI were used for statistical significance. A p value of less 0.05 was considered statistically significant.

Results: A total of 56 patients fulfilled our criteria of ADPKD. There were 40 (71.4%) males and 16 (28.6%) females in our study. The mean age at the time of diagnosis of ADPKD was 47.0 ± 14.5 years. Mean follow up period for all patients was 7.6 ± 4.2 years. Most common form of presentation was hypertension in 38 (67.9%) patients. Kidneys were palpable in 33 (58.9%), liver in 16 (28.6%) and spleen in 6 patients (10.7%). Microscopic haematuria was observed in 38 (67.8%) patients while gross haematuria was present in 10 (17.9%) patients. The murmur of mitral valve prolapse was found in 10 patients on clinical examination which was later confirmed on transthoracic echocardiography (TEE). On MRI/MRA 2 (3.6%) patients each had berry aneurysm and AV malformations.

Three patients (5.4%) received renal transplant and 19 (33.9%) patients were dialysis dependent at the end of study. A total 11 (20%) were lost to follow up. Two patients (3.5%) died during six years follow up. Male sex and uncontrolled hypertension were most important predictors of poor prognosis ($p < 0.03$ and < 0.048 respectively).

Conclusion: Pre-symptomatic patients with ADPKD should be monitored with blood pressure measurements and assessment of their renal function. The advantages of such monitoring include the ability to prevent or control infection and hypertension, to identify potential kidney donors from among the family, to offer advice on marriage and childbearing, and to provide prenatal diagnosis (JPMA 58:305;2008).

Introduction

The autosomal dominant polycystic kidney disease (ADPKD) is an important cause of renal failure, accounting for 10-15% patients who receive haemodialysis.¹ The disease affects about one person per thousand and is the most common form of polycystic kidney disease.² The trait theoretically has a 100% penetrance and 96% of affected persons will manifest the disease clinically by age of 90 years.³ In addition, the disease in general may be more severe and manifest earlier when it is inherited from the mother rather than from the father.⁴ The symptoms or signs of ADPKD typically first occur between the ages of 30-50 years.⁵ These include microscopic and gross haematuria, flank pain, gastrointestinal symptoms due to liver cysts and colonic diverticula, renal colic secondary to clots or stone and hypertension.⁵ Liver involvement is the most frequent extra-renal manifestation.⁶ Aneurysms of the cerebral arteries have been reported to occur in approximately

40% of cases and occasionally may rupture with fatal consequences.⁷

As blood pressure screening has become more widespread, hypertension more than haematuria has become the principal form of presentation.^{8,9} Although control of hypertension to diastolic blood pressure levels of less than 90 mm Hg with conventional antihypertensive agents like diuretics, b-blockers and vasodilators prevents or delays the progression of renal damage,¹⁰ newer antihypertensive agents (Ace inhibitors, ACE receptor-blockers) are more effective^{11,12} in reducing progression to end stage disease. The objective of our study was to characterize clinical presentations and outcomes of APKD in Pakistani patients.

Patients and Methods

Medical records of all patients diagnosed to have ADPKD between January 1997 to December 2003 at the Aga Khan University Hospital, Karachi, were reviewed

retrospectively. Patients were identified using strict clinical criteria. Patients who had family history of ADPKD with evidence of 2 or more cysts in either kidney on diagnostic imaging along with hypertension or renal insufficiency, bilateral polycystic kidneys on diagnostic imaging without family history or unilateral polycystic kidney with evidence of either cysts in liver, berry aneurysm, arterio-venous (AV) malformation and evidence of prior cerebrovascular accident (CVA) on magnetic resonance imaging/angiogram (MRI/MRA) were included.

Medical charts were evaluated for initial presenting complaints, co-morbid, family history of ADPKD, any palpable mass on abdominal examination, cardiac examination for any abnormal finding and use of any anti-hypertensive drugs. For each patient, three measurements of blood pressure were recorded each at least one week apart and mean of these readings was included. Laboratory parameters that were assessed included complete blood count, serum sodium and potassium level, random blood glucose, blood urea nitrogen, serum creatinine, lipid profile, urine detailed report, presence of micro-albuminuria and urine culture. A mean of three readings of serum creatinine, each at least one week apart, was recorded for each patient. An Echocardiogram was also reviewed to confirm cardiac findings. MRI/MRA films were reviewed with an expert radiologist for any presence of berry aneurysm, AV malformation or evidence of prior CVA. Besides confirming presence of polycystic kidneys, diagnostic imaging was also evaluated for the presence of hepatic cyst, splenic cyst, pancreatic cyst, diverticulosis and nephrolithiasis. Dependency on dialysis, renal transplant and death were the final outcomes in our study.

The Statistical package for social science SPSS 10.5 was used for data analysis. Chi square and Logistic regression analyses at 95% CI were used for statistical significance. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant.

Results

A total of 56 patients fulfilled our criteria of ADPKD. There were 40 (71.4%) males and 16 (28.6%) females studied. The mean age at the time of diagnosis of ADPKD was 47.0 ± 14.5 years.

The presenting complaints and co-morbid are enumerated in Tables 1 and 2 respectively. The most common form of presentation was hypertension in 38 (67.9%) patients. Eighteen patients (32%) presented with renal failure (defined as presently elevated serum creatinine (S.Cr) of greater than 1.8 mg/dl for more than

Table 1. Various presenting complaints in 56 patients with ADPKD.

Presenting complaints	Number of patients	%
Hypertension alone	17	30.4
Hypertension with renal failure	11	19.6
Hypertension with flank pain and haematuria	10	17.9
Renal failure	7	12.5
Headache	4	7.1
Renal colic	4	7.1
Diagnosed during routine Screening	3	5.4

Table 2. Co-morbid at the time of presentation in 56 patients with ADPKD.

Co-morbid	Number of patients	%
Ischaemic heart disease	12	21.4
Diabetes mellitus	7	12.5
Nephrolithiasis	6	10.7
Hepatitis B	3	5.4
Epilepsy	2	3.6
Hypothyroidism	2	3.6
Intracranial Bleed	2	3.6
Tuberculosis	2	3.6
Acute myelogenous leukaemia	1	1.8
None	30	53.6

Table 3. Laboratory investigation results in ADPKD patients.

Laboratory Parameters	Mean \pm standard deviation
Haemoglobin	11.2 ± 2.7
White Blood Count	11.2 ± 9.7
Platelets	232.9 ± 94.7
Serum Sodium	136.1 ± 6.0
Serum Potassium	4.1 ± 0.8
Random Blood Sugar	136.5 ± 61.0
Blood Urea Nitrogen	50.3 ± 44.5
Serum Creatinine	4.5 ± 3.2
Serum Triglycerides*	187.5 ± 100.3
Serum Cholesterol*	198 ± 48.0
Serum HDL*	39.3 ± 8.3
Serum LDL*	130.5 ± 38.2

8 weeks. Of these 18 patients, 11 patients had hypertension, whereas 7 were normotensive. The family history of ADPKD was present in 25 (44.6%) patients. The mean systolic pressure was 142.7 ± 23.8 mm Hg and mean diastolic pressure was 86.3 ± 12.4 mm Hg. On clinical examination, kidneys were palpable in 33 (58.9%), liver in 16 (28.6%) and spleen in 6 (10.7%) patients. The murmur of mitral valve prolapse was present in 10 (17.9%) patients. At the time of presentation, 41

(73.2%) patients were on anti-hypertensive drugs; 34 (60.7%) were on beta blockers, 13 (23.2%) angiotensin converting enzyme inhibitors and calcium channel blockers and 10 (17.9%) on diuretics.

The laboratory parameters are summarized in Table 3. On urinalysis proteinuria and glycosuria were present in 40 (71.4%) and 6 (10.7%) patients respectively. Microalbuminuria was present in 7 (12.5%) patients. Hyaline cast was found in only one patient. Gross haematuria was present in 10 (17.9%) and microscopic haematuria in 38 (67.8%) patients; 11 (19.6%) had red blood cells in urine greater than 20 per high power field. White blood cells were present in urine of 41 (73.2%) patients, with nitrite being positive in only 4 (7.1%). Urine culture was positive in 5 (8.9%) patients with 2 having *E. coli* and one each *Klebsiella*, *Pseudomonas aeruginosa* and *Trichosporon beigeli*.

All patients had ultrasound examination of the abdomen on which polycystic kidneys were confirmed. Bilateral polycystic kidneys were present in 38 (68%) cases. Twelve (21.4%) had concomitant cysts in the liver and 7 of these patients had unilateral polycystic kidney. None of our patients had splenic or pancreatic cyst and diverticulosis. The murmur of mitral valve prolapse was confirmed in all ten patients on transthoracic echocardiography (TEE). Additionally, 3 (5.4%) had mild mitral regurgitation and 16 (28.6%) had left ventricular hypertrophy on TEE. On MRI/MRA, 8 (14.3%) patients had evidence of prior CVA and 2 (3.6%) each had berry aneurysm and AV malformations.

The mean follow up period for all patients was 7.6 ± 4.2 years. Three patients (5.4%) received renal transplant and 19 (33.9%) were dialysis dependent at the end of study. The mean interval between presentation and renal transplant was 6.2 ± 4.0 months and the mean intervals between presentation and onset of dialysis was 8.0 ± 4.1 months. Mean S.Cr at presentation in patients requiring renal replacement therapy either in the form of haemodialysis or transplantation during follow up was 7.85 mg/dl (± 3.96) compared to mean S.Cr of 2.05 mg/dl (± 2.04) in patients who did not require renal replacement therapy during follow up ($p < 0.0001$).

Male patients were more likely to be dialysis dependent ($p < 0.03$). Chi square analysis revealed that presence of Ischaemic heart disease ($p < 0.041$), AV-malformation/aneurysm on MRI-MRA, prior CVA ($p < 0.043$) and uncontrolled hypertension ($p < 0.001$) were associated with a poor prognosis. However with Logistic regression analysis (multivariate model) at 95% CI (adjusted for age and sex) only uncontrolled hypertension was found to be independent risk factor associated with a

poor prognosis (< 0.048). Ischaemic heart disease ($p < 0.41$), AV-malformation/aneurysm on MRI-MRA ($p < 0.24$), prior CVA ($p 0.13$) and at presentation ($p < 0.22$) were not found to be independent risk factors associated with poor prognosis.

We could not find any significant association between gender, age at presentation and the presence of liver cysts.

Discussion

ADPKD is the most common form of polycystic kidney disease in which cysts are distributed throughout the cortex and medulla. Although most cases are identified between 30 and 50 years of age,⁵ the condition has been recognized in children¹³ and, therefore, the use of "adult" polycystic disease is inaccurate. The mean age of presentation in our study was 47 years. We believe that the age at diagnosis will decline as more members of families at risk for the trait are screened by genetic testing and by ultrasound examination.

Due to early screening, hypertension has become the most common form of presentation in patients with ADPKD.^{8,9} In a series from Germany, as many as 81% of patients with ADPKD presented with hypertension.⁹ The hypertension alone or in combination with other complaints was present in 67.9% of our patients. ADPKD is an important cause of renal failure requiring haemodialysis.¹ Loin or back pain is had by 50 to 70% of patients with ADPKD.¹⁵ The pain can be colicky, acute or chronic. Colicky pain occurs secondary to the passage of either stones or clots. In our study, only 14 (25%) patients presented with flank pain or renal colic. Renal stones were present in 6 (10.7%) patients which is lower than the earlier finding of 20-30%.¹⁶ Headaches might be due to uncontrolled hypertension or secondary to the presence of berry aneurysms or intracranial bleeding. Cerebral artery aneurysms have been reported to occur in approximately 40% of cases which may rupture occasionally with a fatal consequence.⁷ Only 2 (3.6%) patients had berry aneurysms in our series with additional 2 (3.6%) having AV malformations. One possible explanation for the low prevalence of aneurysms is that a significant number of patients were not subjected to imaging procedures. Mitral valve abnormalities including mitral valve prolapse and regurgitation are common in patients with ADPKD.¹⁷ A significant number of our patients had mitral valve prolapse (17.9%) and mitral valve regurgitation (5.4%).

As patients with ADPKD have an increased renal mass, erythropoietin levels are increased, making anaemia unusual even when end-stage renal disease is present², however, the mean haemoglobin in our series

was 11.2 g/L. In the absence of complications, blood coagulation studies and leukocyte and platelet counts are normal.

Whether insulin resistance and elevations of serum insulin, triglycerides, Low density lipoprotein (LDL) and cholesterol occur in ADPKD-associated hypertension has not been ascertained. Nevertheless, reduced high density lipoprotein (HDL) and elevated LDL levels have been identified as risk factors for renal disease progression in ADPKD.¹⁸ The levels of HDL and LDL in our patients were satisfactory (Table 3).

The early stages of ADPKD usually are not reflected in the urinalysis. Patients with early ADPKD may have a diminished ability to maximally concentrate the urine.¹⁹ Nocturia may be the only symptom of this defect. Massive proteinuria is a rare finding,²⁰ and none of our patients had proteinuria in the nephrotic range. The reason of proteinuria in ADPKD is still unclear; however possible explanation would be damage to capillary endothelium and glomerulosclerosis due to hypertension,²⁵. Haematuria is usually due to rupture of a cyst into the pelvis of the kidney.²¹ Approximately 68% of patients had haematuria on urinalysis with 17.9% had gross haematuria.

Recent studies using sonography or combined sonography and Computerized Tomography (CT scan) indicate that the presence of the disease in young persons can probably be established with a high degree of certainty.¹³ The liver is diffusely cystic in 20-50% of patients with ADPKD.⁶ Women seem to have more severe cystic involvement of the liver.^{6,22} The frequency of liver cysts in our series was 21.4%; however, there was no statistical difference in frequency between men and women. Renal transplant and haemodialysis are now used routinely in end-stage ADPKD. In our study three (5.4%) patients received renal transplant and 19 (33.9%) patients were on chronic haemodialysis.

Our results revealed that presence of Ischaemic heart disease, AV-malformation/aneurysm on MRI-MRA, prior CVA and uncontrolled hypertension were associated with poor prognosis. However with Logistic regression analysis at 95% CI (adjusted for age and sex) only uncontrolled hypertension was found to be an independent risk factor associated with poor prognosis (<0.048).

Manifestations of atherosclerosis like IHD and CVA are one of the leading causes of death worldwide, and the ADPKD induced hypertension, further increases the likelihood of atherosclerotic process.²³ Uncontrolled hypertension is common in patients with autosomal dominant polycystic kidney disease and It may contribute

to cardiovascular risk and to progression of renal failure.

The proportion of male to female patients with ADPKD was 2.5:1 in our group in contrast to 1.8:1 in the Swedish study.¹⁵ Early renal failure requiring dialysis or transplant before 60 years of age was associated with male gender and an early diagnosis of the disease in our study. Gender difference among the population of kidney transplant recipients due to ADPKD has been described¹⁵ in literature. Males have a higher blood pressure due to testosterone²⁴, which results in increased proximal tubular reabsorption and activation of renin-angiotensin-aldosterone mechanism leading to glomerular hypertension and renal injury.²⁵ Men, therefore, have a faster rate of renal growth, more severe hypertension and a faster decline in GFR than women of the same age. On the other hand estrogen deficiency may lead to the development and progression of glomerulosclerosis.

Conclusion

Hypertension, proteinuria and microscopic haematuria are the most common clinical presentations. Compared to females, male patients are more likely to be dialysis dependent ($p < 0.03$). Uncontrolled hypertension was found to be an independent risk factor associated with poor prognosis ($p < 0.048$). In this study majority of patients had poorly controlled blood pressure and presented at a later stage as suggested by mean interval of less than a year between presentation and onset of dialysis.

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