Study of Extrarenal manifestations and Clinico-Radiological Correlation in Autosomal Dominant Polycystic Kidney Disease

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Abstract: Objectives: The objective of this study is to know the prevalence of renal and extra renal manifestations in 50 cases of ADPKD attending King George Hospital, Visakhapatnam, AP between August 2008 and May 2010.

Results: Male to Female ratio is 1.08:1, mean age of patients is 42.1 years (+/-1.4 yr). They were diagnosed as having ADPKD during evaluation of pain abdomen / loin pain in 30% of cases, by family screening in 14% of cases, hematuria in 4% of cases, during the evaluation of hypertension in 4% of cases, during evaluation of fever in 12% of cases, vomiting in 6% of cases. At the time of diagnosis of ADPKD, 58% of patients had hypertension, and palpable kidneys in 64% of patients. Mean hemoglobin at diagnosis was 9.59 +/- 1.39 g/dl, mean proteinuria was 0.56 +/- 0.34 g/day, and mean creatinine was 3.05 +/- 2.61 mg/dl. These patients had liver cysts in 28% of cases, intracranial aneurysm in 4%, diverticulosis in 6%, splenic cysts in 4%, renal calculi in 16%, cyst infection in 16%, cyst hemorrhage in 8%, cyst malignancy in 2%, pancreatic cysts in 6%, ovarian cysts in 16%, MVP in 6%. These patients had a family history in 56% of cases and family history of cerebrovascular accident in 10% of cases.

Keywords: ADPKD, extra renal, liver cysts, aneurysms, cyst hemorrhage.

I. Aims And Objectives

The present study is conducted to evaluate the prevalence of renal and extrarenal manifestations and to correlate the ultrasonographic findings with clinical features in patients with ADPKD.

II. Materials And Methods

The present study was conducted in the Department of Nephrology, Andhra Medical College, King George Hospital, Visakhapatnam, South India between February 2011 and March 2013. Fifty subjects with ultrasonographically diagnosed ADPKD seen in outpatient department or admitted in the department of Nephrology are included in the study, after taking full informed consent. Ultrasonographic diagnostic criteria used are those proposed by Ravine et al 1994.

Ultrasonographic examination is carried out by a single examiner using 3.5 – 5 MHz probe. Detailed history and physical examination are carried out and recorded in the proforma. During history and from previous medical records a note will be made of – all the episodes of renal pain, hematuria, all episodes of upper or lower urinary tract infections with positive cultures, episodes of renal calculi indicated by either passage of stone, presence of stone on plain kidney, ureter, bladder film or ultrasound, the patient’s age when ADPKD was first diagnosed, history of cardiac symptoms or gastrointestinal symptoms, family history of ADPKD or cerebrovascular accidents was recorded.

During physical examination presence of any abdominal masses, abdominal hernias and arterial blood pressure is recorded. Any adult patient is considered to be hypertensive if the untreated blood pressure is > 140/90 mm of Hg or if he or she has been previously diagnosed and treated for hypertension. Chronic renal failure was defined as estimated creatinine clearance of < 90 ml / min (by Cockroft and Gault formula ). End stage renal disease is defined as creatinine clearance < 10 ml/min as estimated by Cockroft and Gault formula (NKF, 2002).

10 ml blood is drawn for biochemical tests which are carried out in renal lab, KGH, Visakhapatnam. Biochemical tests include measurement of blood urea, serum creatinine, calcium. Urine examination includes 24 hr urine protein, microscopic examination of urine. Serum creatinine along with age and weight of the patient was used to estimate glomerular filtration rate by using Cockroft and Gault formula.

Colonoscopy was performed in those patients who had complaints of bloody diarrhea or haematochezia associated with fever and pain abdomen. The procedure was done after the acute episode has subsided. 2D ECHO was performed in all subjects to look for valvular lesions, left ventricular hypertrophy, chamber enlargement, left ventricular ejection fraction and wall motion abnormalities. Magnetic Resonance Angiography of brain was done in selected subjects who gave history of cerebrovascular accident either for...
herself or in the family. A non contrast CT scan of the abdomen was done in subjects in whom cyst infection, haemorrhage or malignancy either on clinical examination or ultrasound abdomen were seen.

### Results

Fifty patients of ADPKD were included in the study. 52% of these were males and 48% were females. Mean age of subjects was 42.12 years and mean age at diagnosis of ADPKD was 40.5 years. Minimum age of the patient when the diagnosis of ADPKD was made was 18yrs and maximum age was 64 yrs. Maximum number of patients were in the age group of 41–50 yrs. Family history of ADPKD was positive in 56 % of all the subjects and family history of CVA was positive in 10% of subjects.

Overall prevalence of hypertension was 58 % among these ADPKD patients. Among males, hypertension was seen in 65.3 % (17/26) and among females in 50% (12/24). Overall prevalence of chronic renal failure among these ADPKD patients was 94% (47/50). Among females prevalence was 96.1% and among males prevalence was 100%. The number of patients in different stages of CKD were CKD 1 – 3 subjects, CKD 2 – 12 subjects, CKD 3 – 13 subjects, CKD 4 – 6 subjects, CKD 5 – 16 subjects. Twenty percent of patients are in ESRD at presentation and started on maintenance hemodialysis. Mean age of ESRD is 41.7 yrs. Minimum age of ESRD patient was 20 yrs and maximum age was 55yrs.

Most common presentation was with hypertension observed in 58 % of patients. Overall, 64 % of patients had palpable kidneys at presentation. Out of 50 patients, 7 cases were detected during family screening and others during evaluation of pain abdomen, mass per abdomen, hypertension, febrile illness or breathlessness. Loin pain was the presenting symptom in 30 % of cases. Thirty percent of patients had azotemic symptoms at presentation(table1). Urinary tract infection was observed in 32 % (16/50) of cases, 10 being male and 6 being female. Haematuria was observed in 12 % (6/50) of cases.

Renal calculi were observed in 18 % (9/50) of patients where 10 % of females and 8% of males had evidence of renal stones. Cyst infection was seen in 16% (8/50) and cyst malignancy in 2% (1/50) of this ADPKD population. Cyst haemorrhage was observed in 8% (4/50) of cases (table 2).

Out of the extrarenal manifestations, liver cysts were seen in 28 % (14/50) of cases. Liver cysts were more common in females (16 %) as compared to males (12 %) (table 3).

Pancreatic cysts were observed in 6 % (3/50) and splenic cysts in 4% (2/50) of this population. Five patients gave history of cerebrovascular accident in the family and another 7 patients gave a history of severe headache and vomitings. Magnetic Resonance angiography performed in these 12 patients revealed small intracranial aneurysms in the anterior circulation in 2 patients.

Although not associated with ADPKD, ovarian cysts were an incidental finding in 16 % of patients.

Mitrval valve prolapse was detected in 6 % (3/50) of cases during routine 2D ECHO.

Colonoscopy performed for various lower gastrointestinal symptoms revealed colonic diverticulosis in 6 % (3/50) of patients.

Mean hemoglobin was 9.59 +/- 1.39 gm/dl and mean serum creatinine was 3.05 +/- 2.61 mg/dl (Fig 14). Sixty four percent of patients had proteinuria out of which 16 % had > 1 gm/day. Mean proteinuria was 0.56 +/- 0.34 gm/dl (Fig 1).

### Correlations

Kidney size was correlated with various clinical parameters. Depending on kidney size, all the subjects were divided into 6 quartiles. Quartile 1 - 11 – 13 cm, Quartile 2 - >13 – 15 cm, Quartile 3 - >15 – 17 cm, Quartile 4 - >17 – 19 cm, Quartile 5 - >19 – 21 cm, Quartile 6 - >21 cm. As the size of the kidneys increased, the serum creatinine also increased, which was significant (p = 0.0015) (Fig 2).
The larger the kidneys, the higher was the proteinuria which was significant ($p = 0.0035$).

Chi square test showed significant correlation between kidney size and hypertension ($p = 0.0005$).

**Fig 3** showing significant correlation between kidney size and proteinuria ($p = 0.0035$).

**Fig 4** Chi square test showing significant correlation between kidney size and hypertension ($p = 0.0005$).
Chi square test also showed significant correlation between kidney size and requirement of dialysis (p = 0.0028) (Fig 10).

However, there was no correlation between kidney size and serum albumin. Also, kidney size does not correlate with hemoglobin.

Chi-square 18.093
DF 5
Significance level P = 0.0028
Contingency coefficient 0.515

Fig 5: Kruskal Wallis test showing significant correlation between kidney size and proteinuria

Fig 6: Chi square test showing correlation between kidney size and requirement of dialysis (P = 0.0028)

Fig 7: Box and Whisker Plot showing no correlation between kidney size and serum albumin (p = 0.75)
Fig 8 Box and Whisker plot showing no correlation between kidney size and hemoglobin (p = 0.118)

Fig 9 Histogram showing mean haemoglobin (9.59 +/- 1.39 gm/dl)

Fig 10 - Histogram showing mean serum creatinine at presentation
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IV. Discussion

ADPKD is a common genetic disorder, most common and serious sequelae of this disease is ESRD. The various renal and extrarenal manifestations of the disease have been extensively studied. Present study has analysed the clinical profile of fifty ADPKD patients and tried to establish correlation of various clinical parameters with radiologically estimated pole to pole kidney size.

In the present study, male to female ratio was 1:1, in previous studies it was 1:2. Mean age of diagnosis in this study was slightly higher (40.5 %) than previous studies (35.1 %). Hypertension was prevalent in 58 % of this cohort of ADPKD patients, slightly less compared to previous studies which had a prevalence of 63 to 80 %. In this study, the prevalence of hypertension was 33 % in patients with CKD stage 1, 65 % in CKD stage 3, and 66 % in CKD 4. In this study, the most common mode of diagnosis was during evaluation of abdominal pain / loin pain. Most common clinical feature was hypertension. Most common renal complication was urinary tract infection (32 %), which correlated with previous studies. In this study urinary tract infection was more common in males in contrast to previous study which showed UTI to be more common in females.

Haematuria, gross and microscopic have been described to be present in 50 % of patients, it is the presenting symptom in 35 % of ADPKD patients. In the present study, gross haematuria was seen in 12 % and microscopic hematuria in 6 % of patients. Gross hematuria was equally common in males and females, whereas, microscopic hematuria more common in females. Risk factors earlier described for gross hematuria are hypertension and increased renal size.

Nephrolithiasis was described in 20 % of patients with ADPKD. In the present study, prevalence of nephrolithiasis was 18 % and more common in males. Proteinuria has been observed in one third of ADPKD patients, and is almost always mild. In this population, proteinuria was found to be more prevalent (64 %), and only 16 % of these had proteinuria of > 1 gm / day. Proteinuria was greater in males and in those with larger kidneys. Cyst malignancy was detected by CT abdomen in one patient, who later on succumbed to severe renal failure. Among extrarenal manifestations of the disease, liver is the most common organ to be affected by cysts. Approximately 50 % of patients without azotemia have hepatic cysts and prevalence increase with age. Prevalence of hepatic cysts in the present study was 28 %, slightly less than previous studies. In the present study, liver cysts were more common in females (16 %), and in patients with ESRD. All patients with liver cysts had no symptoms of liver disease and tests for liver function were normal.

Pancreatic and splenic cysts were seen in 16.7 % and 6.7 % respectively in previous studies. In the present study, the corresponding values were 6 % and 4 %.

Family history of cerebrovascular accident was seen in 10 % patients. MR angiography of brain revealed intracranial aneurysms in 4 % of cases which correlates with previous studies. In a Brazilian study, intracranial aneurysms were seen in 3 out of 92 ADPKD patients. Previous studies showed colonic diverticula in 3.3 % of cases. In the present study colonic diverticula were seen in 6 % of patients.

Routine 2 D ECHO in all the fifty ADPKD patients revealed Mitral Valve Prolapse in 6 % of cases. One case was associated with mild Mitral insufficiency, the same patient had congestive heart failure but not due to valvular lesion. Earlier studies have described that 45 % of patients of ADPKD will reach ESRD by the age of 60 yr 7, 92. However considerable variability in the age of ESRD has been shown to have less aggressive course in females than males 7,17 and hypertension is a major factor associated with more aggressive course of renal disease 7. Other factors described to be independently related to earlier onset of renal insufficiency in both sexes are presence of gross and microscopic hematuria and occurrence of more severe proteinuria 7.

Prevalence of chronic renal failure in the present study was 94 % and 21 % of these patients had ESRD. The prevalence of renal insufficiency was more in males.

Kidney Size And Progression Of Renal Disease : Renal enlargement is a hallmark of ADPKD. Evidence indicates that progressive increase in renal size in ADPKD is primarily due to accumulation of fluid within cysts leading to increase in cyst size. Increase in cyst volume is responsible for ultimate decline in glomerular filtration rate, that is the feature of ADPKD.

The average age of diagnosis of ADPKD is 27 yrs and hypertension is 31yrs, before loss of renal function. Once renal dysfunction occurs, a universal rapid decline in renal function (approx 5.9 ml/min/yr) occurs. Food and Drug Administration acceptable outcome measures of progressive renal disease include frequency or time to ESRD, doubling of serum creatinine, or death. All of these outcome measures are ineffective with little or no role in ADPKD due to long presymptomatic phase and late age of onset of renal dysfunction in this disorder. Currently changes in serum creatinine are monitored to determine the extent of disease progression and to assess prognosis. However, serum creatinine donot typically rise in patients with ADPKD until 4th to 5 th decade of life, when massive enlargement has occurred. Franz and Reubi developed a model of curvilinear relationship between kidney size and function, indicating that significant renal enlargement

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takes place before loss of kidney function in ADPKD. Kidney function does not decline in individuals with ADPKD until kidney size is at least 5 times normal.

In the present study, cheap and widely available investigation ultrasonography was used to measure pole to pole length of the kidney. Because of the high interobserver variability in measurement of kidney size, a single observer performed all the scans. Larger kidneys correlated with higher proteinuria, hypertension and higher creatinine. This study could not do any correlation between kidney size and serum albumin and hemoglobin.

V. Conclusions

ESRD is the most serious complication of ADPKD. Recent data suggests that the objective test to assess disease progression is estimation of kidney size. Although MRI is the best method to assess the renal volume accurately but it is expensive and time consuming. Ultrasonography is the viable option for MRI. Due to its non-invasiveness it can be repeated any number of times to monitor the size of kidneys and other extrarenal manifestations and complications hence it is used. Increased renal size predicts more proteinuria, loss of renal function, hypertension, and progression to ESRD. So, it is reasonable to justify kidney size as a marker of disease severity. Ability to monitor the disease progression accurately will improve the ability to demonstrate efficacy of potential therapies and will also allow to target treatment at those patients who are most at risk. And once effective therapies for ADPKD are developed, these are likely to be effective early in the course of disease and then screening patients at risk of ADPKD may become more prudent.

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Table 1

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<td>Loin pain</td>
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<tr>
<td>Azotemia</td>
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<td>Edema</td>
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<td>Hypertension</td>
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<td>Urinary symptoms</td>
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Table 2

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<td>Cyst infection</td>
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<td>Cyst malignancy</td>
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<tr>
<td>Cyst hemorrhage</td>
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<tr>
<td>Renal calculi</td>
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Table 3

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