Clinical presentation and outcome of autosomal dominant polycystic kidney disease in Nigeria

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Abstract:

Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is presumably rare in Africa. Knowledge about the disease in Nigeria is limited as demonstrated by scanty articles on the subject.

Objectives: To determine the pattern of clinical presentation and outcome of ADPKD among ADPKD patients.

Method: ADPKD subjects were prospectively studied between January 1996 and December 2010. Their demographics, clinical and investigation parameters were documented. Dependency on dialysis, renal transplant and death were the final outcomes.

Results: Forty one patients (M:F=1.3:1) with mean age of 48.6±4.6 years were studied. ADPKD was diagnosed at 2.73 cases per annum. Family history of ADPKD and hypertension were present in 56.1% and 82.9% respectively. Their mean systolic and diastolic blood pressures were 166.9 ±23.6 and 104 ±21.2 respectively.

Nocturia (78.0%) and loin pain (68.3%) were the most common presenting symptoms. Liver cysts (31.7%) and aortic regurgitation (22.0%) were the predominant extra-renal manifestations.

Twenty three (56.1%) received haemodialysis; no renal transplantation. Death rate was 51.2%. Presence of uraemia and intra-cerebral aneurysm contributed significantly to mortality.

Conclusion: ADPKD may not be so rare in Nigeria. Awareness campaign to change attitude of family members to screening and further studies using newer criteria for diagnosis of ADPKD should be conducted.

Keywords: Clinical presentation, autosomal dominant polycystic, kidney disease, Nigeria.

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Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the commonest form of genetically inherited kidney diseases with a prevalence rate of 1:400 to 1:1,000.[1] It is generally assumed to be rare among Blacks in Africa.[2,3] It ranks as the third leading cause of End Stage Renal Disease (ESRD) and accounts for 5-13.4% of patients undergoing haemodialysis in the United States and Europe.[4-6]

In most developed economies, the diagnosis of ADPKD is now made as early as in the first decade of life due to advancement in gene technology contrary to resource-poor settings such as sub-Saharan Africa where the diagnosis of ADPKD is still restricted to clinical judgement and renal ultrasound. This has hampered knowledge about the disease in our setting as demonstrated by the few studies and case reports that have been published on ADPKD in Nigeria to date.[7-9]

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We therefore set out to determine the pattern of clinical presentation and outcome of ADPKD among patients who presented to our renal unit.

Method

Consecutive patients that satisfied the inclusion criteria for ADPKD were prospectively followed up over a period of 15 years (January 1996 - December 2010) at the renal unit, Obafemi Awolowo University Teaching Hospital, Ile-Ife after due approval from the Research and Ethics Committee.

Clinical and laboratory evaluations (including medical history, physical examination and cardiac examination using echocardiogram (Vivid 7, General Electronics, USA) were conducted. The diagnosis of ADPKD was established using the Ravine criteria[10], presence of hypertension, multiple liver cysts and family history of cystic kidney disease. Patients with renal cysts who did not fulfill the Ravine criteria,patients aged <18 years, those with renal malignancy, exophytic cysts, calcifications, tuberous sclerosis, or acquired simple cysts were excluded.

Pre-dialysis blood samples were obtained and assessed for full blood count and serum chemistry. Urinalysis and urine culture were carried out on samples collected under standard techniques. The glomerular filtration rate (eGFR) was estimated using the Cockroft and Gault formula.[11]

Ultrasound scan of the abdomen was conducted to search for presence of solid organ cysts. Cranial Computerised Tomography Scan (CAT scan) or Magnetic Resonance Imaging (MRI) were employed where necessary to rule out presence of intra-cranial aneurysm (ICA). Autopsy was carried out on all subjects who died during the study after due consent from family members. Dependency on dialysis, renal transplant and death were the final outcomes in this study.

Data was analysed using SPSS statistical software version 17. Continuous variables were expressed as mean±SD, median and range. Chi square testing was carried out to determine significance (p value < 0.05 at 95% Confidence Interval).

Results

A total of 41 patients fulfilled the diagnostic criteria. They included 23 (56.1%) males and 18 (43.9%) females (M:F=1.3:1). Their age range at the time of diagnosis was 18-80 years with mean age of 48.6±4.6 years. The median (range) follow up period for all patients was 24 (0.25-84) months. The peak age at presentation of ADPKD was between 31-40 years (table 1).

Table 1: Parameters of ADPKD subjects in OAUTH Ile-Ife (1996-2010)

PARAMETERS	MALE	FEMALE	ALL SUBJECTS
Baseline parameters	**mean ±SD**	**mean ±SD**	**mean ±SD**
Age at presentation (years)	43.4 (±15.7)	46.3 (±14.3)	48.6±4.6years
SBP (mmHg)	162.8 (±26.7)	172.2 (±18.3)	166.9 ±23.6
DBP (mmHg)	104.7 (±23.6)	104.4 (±18.5)	104 ±21.2
Sodium (mmol/L)	133.2 (±5.9)	135.5 (±3.8)	134.2±5.1
Potassium (mmol/L)	4.8 (±1.1)	4.4 (±0.9)	4.5±1.0
Bicarbonate (mmol/L)	20.5 (±2.3)	20.9 (±2.5)	20.6±2.3
Urea (mmol/L)	18.8 (±9.9)	20.5 (±14.0)	19.5±11.7
Creatinine (umol/L)	707 (118-2413)	484 (76-3722)	614 (76-3722)
eGFR (ml/min)	33.2 (±22.2)	35.5 (±25.8)	34.2±23.6
Haematocrit (%)	27.0 (±4.8)	25.9 (±6.1)	26.5±5.4
TWCC	5,472.6 (±2344.9)	5,789.3 (±2412.5)	5,611.6±2,350
Platelet	180,671.7 (±30,233)	214,777.8 (±139,605.9)	195,645.1±95286.6
No of HD sessions	5.4 (±5.0)	6.0 (±5.2)	5.6±5.0
Duration of survival (mo)	24.0 (±24.0)	23.2 (±20.9)	23.6±22.4
Age at death (years)	46.6±15.8	45.9±14.1	46.3±14.7
Age of survivors (years)	44.4±16.7	50.3±14.8	47.1±15.8
Age range, years (N=41)	**N (%)**	**N (%)**	**N (%)**
15-20	3 (100%)	0	3 (7.3%)
21-30	1 (25%)	3 (75%)	4 (9.8%)
31-40	7 (63.6%)	4 (39.4%)	11 (26.9%)
41-50	4 (44.5%)	5 (55.5%)	9 (21.9%)
51-60	6 (66.7%)	3 (33.3%)	9 (21.9%)
61-70	1 (33.3%)	2 (66.7%)	3 (7.3%)
>70	1 (50%)	1 (50%)	2 (4.9%)
JNC hypertension stage (N=41)			
pre-hypertension	3 (7.3%)	0	3 (7.3%)
stage 1	4 (9.8%)	3 (7.3%)	7 (17.1%)
stage 2	16 (39.0%)	15 (36.6%)	31 (75.6%)
Hypertension by age (N=38)			
15-20	3 (7.9%)	0	3 (7.9%)
21-30	1(2.6%)	3 (7.9%)	4 (10.5%)
31-40	6 (14.8%)	4 (10.5%)	10 (26.3%)
41-50	3 (7.9%)	5 (13.2%)	8 (21.1%)
51-60	5 (13.2%)	3 (7.9%)	8 (21.1%)
61-70	1 (2.6%)	2 (5.3%)	3 (7.9%)
>71	1 (2.6%)	1 (2.6%)	2 (5.3%)
Haematocrit % (N=41)			**frequency**
<20	2 (4.9%)	5 (12.2%)	7 (17.1%)
20-29	14 (34.2%)	9 (22.0%)	23 (56.1%)
30-39	7 (17.1%)	4 (9.8%)	11 (26.8%)
≥40	0	0	0

SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; N, frequency; PCV, packed cell volume; TWCC, total white cell count; HD, haemodialysis; [#]median/range

Their baseline parameters are presented in table 1. Their mean systolic and diastolic blood pressures were 166.9 ±23.6 and 104 ±21.2 respectively with a median serum creatinine of 844μmol/L (range 76-3,722 μmol/L). Their mean estimated glomerular filtration rate was 34.2±23.6ml/min/1.73m^2.

Nocturia (78.0%), loin pain (68.3%) and facial swelling (61.0%) were the most common presenting symptoms (table 2). Liver cysts (31.7%), aortic regurgitation (22.0%) and cerebral aneurysms (14.6%) were the most common extra-renal manifestations (table 2).

Table 2: Renal and extrarenal manifestations of ADPKD subjects in OAUTH Ile-Ife (1996-2010)

Parameter	Total	Frequency by gender	
Complaints	**Frequency (%)**	**Male**	**Female**
Nocturia	32 (78%)	19	13
Frothy urine	2 (4.9%)	1	1
Facial swelling	25 (61%)	12	13
Body swelling	10 (24.4%)	4	6
Loin pain	28 (68.3%)	16	12
haematuria	15 (36.6%)	7	8
LOC	4 (9.8%)	1	3
Oliguria	24 (58.5%)	14	10
Stroke	4 (9.8%)	2	2
Renal findings			
Pallor	35 (85.4%)	18	17
Hypertension	36 (87.8%)	19	17
Hepatomegaly	4 (9.8%)	1	3
Nephromegaly	34 (82.9%)	18	7
LVH	35 (85.4%)	18	17
Uraemia	24 (58.5%)	14	10
Splenomegaly	1 (2.4%)	0	1
UTI	13 (31.7%)	6	7
Cystic haemorrhage	14 (34.2%)	8	6
Extrarenal findings			
Liver cysts	13 (31.7%)	6	7
Splenic cyst	1 (2.4%)	0	1
Pancreatic cyst	2 (4.9%)	1	1
Aortic regurgitation	9 (22%)	4	5
MVP	0	0	0
Cerebral Aneurysm	6 (14.6%)	3	3
Ovarian cyst	0	0	0

LOC, loss of consciousness; LVH, left ventricular hypertrophy; UTI, urinary tract infection; MVP, mitral valve prolapsed

Fourteen (34.1%) experienced cystic haemorrhage. recurrent urinary tract infection was found in 13 (31.7%). End Stage Renal Disease was present in 19.5% of the subjects (figure 1).

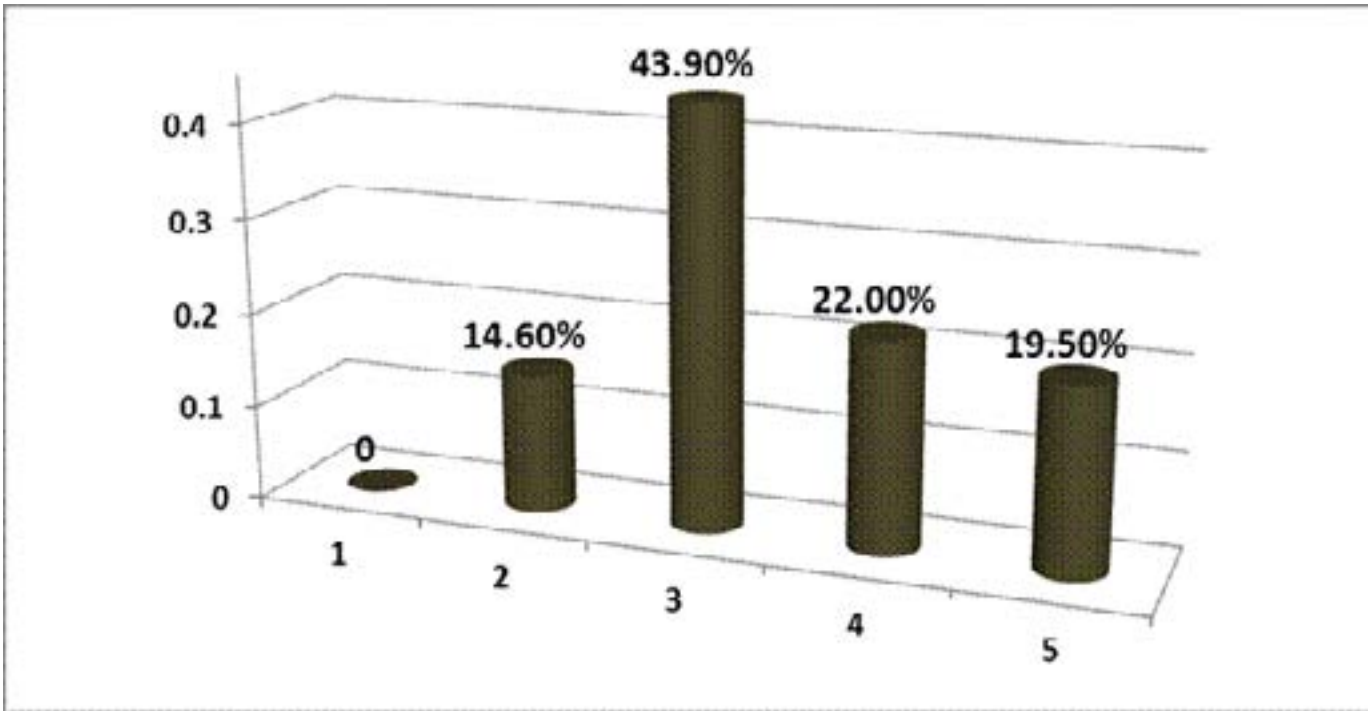

Figure 1: KDOQI staging of ADPKD patients in OAUTH Ile-Ife (1996-2010)
HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy

A range of 1 to 7 cases were diagnosed at an average of 2.73 cases per annum (table 3). The progression of ADPKD peaked in 2006-2007 and then dropped momentarily (table 3).

Table 3: Annual incidence of ADPKD in OAUTH Ile-Ife (1996-2010)

Year of presentation	Male	Female	Total
1996	0	1	**1 (2.4%)**
1997	1	1	2 (4.8%)
1998	1	1	2 (4.8%)
1999	0	2	2 (4.8%)
2000	0	1	1 (2.4%)
2001	3	0	3 (7.5%)
2002	3	0	3 (7.5%)
2003	1	0	1 (2.4%)
2004	0	2	2 (4.8%)
2005	2	1	3 (7.8%)
2006	3	4	7 (17.1%)
2007	4	3	7 (17.1%)
2008	3	1	4 (9.8%)
2009	1	1	2 (4.8%)
2010	1	0	1 (2.4%)
Total	23	18	41 (100%)

Twenty four (58.5%) subjects presented with renal failure. Twenty three (56.1%) of them volunteered family history of chronic kidney disease. Thirty four (82.9%) had family history of hypertension. However, we could only confirm family history of kidney disease in 3 of the subjects because of reluctance of first degree relatives to participate in screening for ADPKD.

Twenty three (56.1%) received haemodialysis while none received renal transplant within the study period (figure 2). Among the 21 subjects who died during the study period, 6 (28.6%) had autopsy-confirmed complications arising from ruptured intra-cerebral aneurysm.

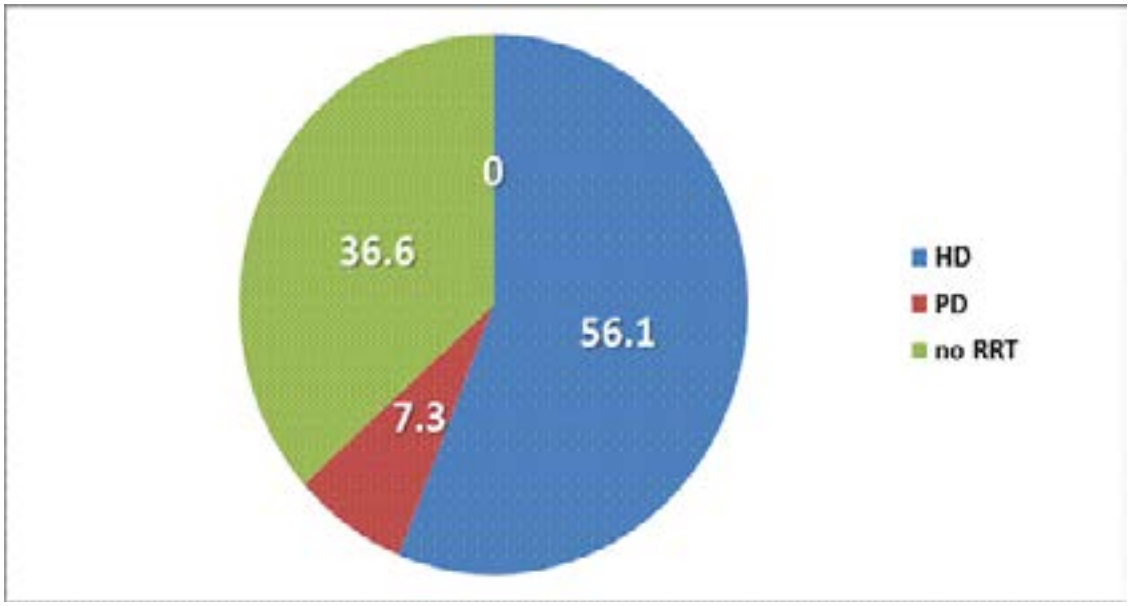

Figure 2: Utilization of renal replacement therapy by ADPKD patients.

The average age at death and survival with respect to gender are as shown in table 1. The mean survival was higher among women. The presence of uraemia and intra-cerebral aneurysm contributed significantly to mortality (table 4).

Table 4: Factors contributing to mortality among ADPKD patients in OAUTH

Mortality factors	Alive	Dead	p value (CI, 95%)
Uraemia	6	18	<0.01
Ruptured cerebral aneurysm	0	6	0.01
Female gender	9	9	0.89
Male gender	11	12	0.89
Left ventricular hypertrophy	15	20	0.067

Discussion

General and renal manifestations

Demography: The male predominance and mean age of 48.6±4.6 years compares with findings by Chijioke et al and other authors.[7,12] The peak age of incidence of ADPKD in our study (3rd and 4th) decade of life was a bit earlier than 4th to 5th decade found by Chijioke et al.[7] However, since the advent of genetic mapping, the diagnosis of ADPKD may be made as early as infancy and in-utero.[13]
A family history of cystic kidney disease was found in 56.1% which is comparable to about 60% earlier reported.[14-15] However, first degree relatives of only seven of the subjects consented to screening for ADPKD. Three of such family groups were found to have members with history of cystic kidneys verified by history, physical examination and ultrasonographic criteria for diagnosis of ADPKD.

Renal symptoms: Nocturia and loin pain were the most common symptoms in our study. Nocturia results from inability of renal tubular cells to re-absorb salt and water and may present with normal or increased urine volume.[11] It is often obtained after a careful history taking by the physician. Loin pain, on the other hand, was the main presenting complaint at presentation (68.3%) and is slightly higher than about 60% quoted by Bajwa et al.[16] Acute loin pain (uni- or bilateral) may arise from cystic haemorrhage, urolithiasis, mass pressure effect and urinary tract infections.
In our study, 31.7% had urinary tract infection which is similar to 35.8% reported by Romao et al.[17] It was more prevalent among females in conformity with findings by previous authors.[7,17-19]

Majority of the subjects (73.2%) had haematocrit below 30%. This is lower than 88.2% reported among an elderly group with ADPKD.[21] The high prevalence of anaemia in our study may be linked to late presentation to the hospital as shown by 85.4% presenting between KDOQI stages 3-5 CKD. Helal et al reported uraemia among their subjects at presentation.[20] This may also account for the absence of polycythaemia (commonly associated with cystic production of erythropoietin) in our subjects.
Hypertension was highly prevalent in this study. It was higher than 73% found byAlves et al. and can reach up to nearly 100% of ADPKD patients with ESRD.[18,21] Majority of our patients presented with severe hypertension. It was more common among men (56.1%) in our study. In Dakar, hypertension was found in 61.1% of their male subjects who had ADPKD even though some other studies reported higher prevalence of hypertension among women.[7,17-18,22]
Hypertension is known to occur at an earlier age in patients with ADPKD compared to the general population.[21] The peak incidence of hypertension was 31-40 years in our study which coincides with the peak age at presentation of ADPKD. This is similar to diagnosis of hypertension among male and female ADPKD subjects aged 32 and 34 years respectively by Schrier et al.[23]
Left ventricular hypertrophy (LVH) was found in 85.4% of all subjects, higher than 73% reported by Chapman et al.[24] The occurrence rate of LVH was higher among our normotensive (40% vs 23%) and hypertensive (91.7% vs 48%) subjects when compared to findings by Chapman et al.[24]
Four (9.8%) of our subjects presented with loss of consciousness with radiological imaging revealing a diagnosis of haemorrhagic stroke in three of them. Stroke was found to occur in 7.6% of subjects in Brazil[17] and has been associated with severe hypertension and anuerysmal sub-arachnoid haemorrhage in ADPKD patients.

Extra-renal presentations

Solid organ cysts: Polycystic liver disease ranks as the commonest extra-renal affectation by ADPKD and can occur in more than 80% of adults with the disease.[25] We found that 31.7% of our subjects had polycystic liver which is similar to 31.9% and 32.4% reported previously.[17,20] A lower incidence of 10.4% was reported by Alves et al in Brazil among elderly subjects.[18] The occurrence of liver cysts (attributed to oestrogen-induced cystic expansion and multiplication) was higher among females in this study as previously reported by other authors.[17,20,26]

Cardiac valve anomalies: In our study, aortic regurgitation (AR) was the only cardiac anomaly detected by echocardiogram. The prevalence was higher than 8% and 19% reported earlier.[27-28] AR can co-exist with other cardiac-specific anomalies such as mitral valve prolapse, mitral incompetence, tricuspid incompetence and tricuspid valve prolapse.[27-28]

Intra-cerbral aneurysms (ICA): Dunger was the first to report the association between ADPKD and ICA in 1904.[29] Intra-cerebral aneurysms generally occur in 9–12% of ADPKD patients compared to 2–3% in the general population.[30] Here, we report an occurrence rate of autopsy-confirmed ICA of 14.6%. Previous autopsy series reported prevalence ranging between 2.3% and 19.7%.[31-32] Other authors who used Computer Tomographic scan and magnetic resonance imaging reported occurrence rates of between 4.5% and 10.8%.[33-35]

ICA ruptures: Rupture of aneurysms is the most serious complication in ADPKD and may account for 7% to 13% of deaths in ADPKD.[36] The average age of ICA rupture was 49.2 years in our study, higher than 41 years reported by Rivera et al.[37] Only two of the subjects with ruptured ICA were diagnosed clinically. This might have been due to the sparing use of angiographic technology in our study owing to technicalities and costs.

Other extra-renal manifestations: We were able to demonstrate splenic and pancreatic cysts in our subjects but there was no evidence of abdominal hernia or diverticular disease. One author reported cysts in seminal vesicle, pancreas and arachnoid membrane as well as spinal meningeal and connective tissue abnormalities such as abdominal hernia and diverticular disease.[38]

Renal replacement therapy: More than half of our subjects entered into dialysis with haemodialysis as the predominant modality. Peritoneal dialysis (PD) is considered to be more frequently used and to be associated with better survival in ADPKD patients.[39] In resource-poor settings however, haemodialysis is the preferred option due to scarcity of PD fluids, and associated high costs and complications. None of the subjects received kidney transplant due to costs and non-availability of volunteer donors.

Outcome: Mortality was 51.2% in our study. This is over two times the figure reported by Chijioke et al.[7] Mortality was higher among males, similar to other findings.[40-41] Specific causes of death could not be determined as we did not conduct autopsy for all subjects. The presence of uraemia and intra-cerebral aneurysm was associated with mortality. Dalgaard identified uraemia and cerebral haemorrhage as the commoner causes of death in a cohort of ADPKD subjects.[42] Other factors that have been associated with mortality in ADPKD patients include cardiac disease and infections.[40,43-44]

Conclusion

The clinical presentation and outcome of ADPKD are comparable to patients from other parts of the world. There is a need for (i) public enlightenment in order to encourage relatives of ADPKD patients to comply with screening for ADPKD and, (ii) high-powered, multi-centred studies that should include use of gene technology for pre-natal and early childhood diagnosis.

Conflict of interest

No conflict of interest.

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