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CLINICAL REVIEW

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: CURRENT TREATMENT AND FUTURE THERAPEUTIC OPTIONS

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. Cyst initiation and expansion arise from a combination of abnormality in cell proliferation, secretion of fluid and extracellular matrix defects. The consequence is kidney enlargement and interstitial fibrosis. The disease has extra-renal manifestations including polycystic liver disease, intracranial aneurysms, cardiac valve defect and development of cyst in many other organs. This clinical review focused on existing treatment and future therapies in ADPKD using a clinical scenario in a developing world. We report a 49 year old woman who presented to the nephrology clinic with abdominal pains, recurrent painless haematuria and generalized body weakness. She was found to have ballotable kidneys, hypertension and uraemia. There was a radiologic confirmation of polycystic kidneys with extra-renal cysts in the liver. This clinical review draws attention to this cause of chronic kidney disease, current treatments and promising therapies.

INTRODUCTION

Autosomal dominant polycystic kidney disease (APKD) is a multi-systemic disorder characterized by the development of multiple bilateral renal cysts and associated with cysts in other organs, such as liver, pancrease, and arachnoid membrane.[1] It is a genetic disorder caused by mutations in one of two different genes; *PKD1* (85%) or *PKD2* (15%) and is

expressed in an autosomal dominant pattern, with variable expression.[2] Autosomal dominant polycystic kidney disease is also associated with liver ductal cysts, hypertension, chronic pain and extra-renal problems such as cerebral aneurysms.[2] It has been described in all races[3] with similar incidence rates in white and black American patients undergoing dialysis.[4-5] The prevalence of ADPKD is 1:400 to 1:1000 and thus it affects approximately 12.5 million people worldwide.[4]

Unlike most other chronic kidney disease (CKD), polycystic kidneys enlarge over time and total kidney volume (TKV) as measured by magnetic resonance imaging (MRI) can exceed 1500 ml compared with 300–400 ml in healthy controls.[5] Cyst initiation and expansion arise from different processes including abnormal cell proliferation, fluid secretion and extracellular matrix defects. All these results in kidney enlargement and interstitial fibrosis.[5] By the age of 60 years, half of all ADPKD patients require dialysis or transplantation.

The aim of this clinical illustration is to emphasize that it is a common cause of end-stage renal disease in Nigeria, there are currently no effective treatments to slow disease progression, and understanding the genetic defect and the function of the ADPKD proteins, polycystin-1 (PC-1) and polycystin-2 (PC-2) have revealed new therapeutic targets.

CASE ILLUSTRATION

The index case is a 59 year old woman who was referred to the Nephrology clinic of our hospital from a private hospital in Lagos due to her relocation. She however, did not present to the clinic until 13 months thereafter. She presented to the clinic with generalized body weakness of 4 months duration, fever, abdominal pain and recurrent haematuria of 3 weeks duration.

She was apparently well until 4 months ago when she started having generalized body weakness preventing her from doing her daily activities. She has no history of loss of appetite, nausea or vomiting. No yellowish discolouration of eyes or pruritus. No history of breathlessness and no chest pain. The fever started 3 weeks before presentation. It was continuous, temporarily relieved by analgesics. There was associated abdominal pain which was a mild dull ache, worse at loin area with no radiation. It was continuous and no known aggravating or relieving factor. There was history of 3 episodes of haematuria which were total, painless and not associated with clots or passage of stone. No occurrence of dizziness after urinating. Each episode self terminates after the patient urinates the third or fourth time in a day, and recurs after 3 or 4 days. No history of trauma to the abdomen or loin area and no associated abdominal swelling. There was no history of facial or bilateral leg swelling, rashes on the skin joint pains or swelling and no history of recurrent headaches. There was no history of vomiting, puritus, hiccough, irrational behavior or seizures. She was diagnosed hypertensive six months ago in the general outpatient department, was commenced on Alpha methyl-dopa and Amlodipine but was not compliant to medications with no reason for non compliance. She was not a diagnosed diabetic, no history of use of mercury-containing cosmetics, herbal remedies or

chronic use of analgesics. No family history of kidney disease. She is the 2nd of 5 children in a monogamous family. She is also married with 6 children. There is no family history of hypertension, diabetes or kidney disease. He does not take alcohol or tobacco in any form. The referral GFR was 52mls/min/1.73m^2, blood pressure of 130/80mmHg and stable clinical condition, she also had an ultrasound report showing bilateral multiple cysts in the kidneys.

EXAMINATION

On examination, she was not ill looking, was pale, febrile (38.9^{o}C), acynosed, not dehydrated. There was no finger clubbing or ankle oedema. The abdomen was flat, soft, moves with respiration. There was no area of tenderness, the liver and spleen were not palpably enlarged but both kidneys were bimanually ballotable. There was no ascites. The blood pressure was 190/100 mmHg. The apex beat was undisplaced with a normal first and second heart sounds. She was conscious, well oriented in time, place and person and had flapping tremors. Fundoscopy showed normal eye findings- no evidence of hypertensive eye changes. Urgent urinalysis done in the clinic showed protein = 2+, blood = 2+, nitrite = positive, ph = 6.0, specific gravity = 1.010.

Based on the history, physical examination and ultrasound finding the diagnosis of chronic kidney disease secondary to autosomal dominant polycystic kidney disease complicated by haematuria and urinary tract infection was made. She was admitted into the ward and investigations requested for.

INVESTIGATION RESULTS

Abdominal ultrasound: Figures 1 and 2 showed that both kidneys were markedly enlarged measuring 14cm x 6cm for the left and 15cm x 5.5cm for the right. Both contain multiple, oval shaped, thin walled, anechoic cysts distorting the architecture of the kidneys completely. The liver was also grossly enlarged with multiple oval-shaped thin walled cysts with preservation of the liver architecture (Fig. 3).

Chest X-ray and ECG were essentially normal. Echocardiography showed concentric left ventricular hypertrophy with no evidence of valvular disease. Urine microscopy- showed 2-3 red cells / hpf, 0-1 epithelial cell / hpf and triple phosphate crystals, gram negative cocci, culture yielded growth of Escherichia coli sensitive to ciprofloxacin. Other laboratory investigations done by the patient are as shown in table 1.

She had a session of haemodialysis (first session) same day with one unit of blood transfused intradialysis. She was placed on IV 0.9% Normal saline infusion 1 Litre 12 hourly, Tabs Ciprofloxacin 500mg bd, Tabs Lisinopril 5mg daily, Tabs Amlodipine 10mg daily, Tabs Frusemide 40mg daily, Tabs vitamin D_3 25 microgram daily, calcium carbonate 600mg tds, simvastatin 20mg nocte, ferrous sulphate 200mg b.d, vitamin c 100mg tds, vit b 1 tds, folic acid 5mg daily. She was counseled on the nature of disease, likely course of progression and management plan. She was also counseled on dietary restriction of fats was placed on low salt and protein diet.

The patient improved remarkable improvement after 11 days with absence of

fever and the episodic haematuria, good blood pressure control, and improvement in body weakness. She had a total of four sessions of haemodialysis at intervals of two days. She was counseled on the nature of her illness and the need to bring all her children and close family relatives for screening to detect asymptomatic cystic kidney disease. One of the first degree relatives aged 39 years was found with polycystic kidney disease and was booked for follow up visits. She was also counseled on the need to avoid strenuous activity such as contact sports to avoid trauma to the kidney and haematuria.

She was discharged after 13 days on admission for out-patient follow up. She was on twice weekly haemodialysis for the first three weeks through a internal jugular access. The nature of the CKD was clearly end-stage and this was properly communicated to her. She had an arteriovenouis fistula created on the left fore-arm and since then had been on dialysis and regular follow up.

DISCUSSION

Autosomal dominant polycystic kidney disease occurs worldwide and in all races. The worldwide prevalence is estimated at approximately 1 in 400 to 1 in 1000 live births.[6] In most patients, however, the diagnosis is made decade later, and in some patients are never diagnosed. Therefore at any point in time, only a fraction of genetically affected individuals are aware of having the disease. Previously, data are very limited in black Africans suggesting lower prevalence rate of ADPKD in this part of the world. However with widespread availability and increased use of imaging techniques recent reports showed it is relatively common and commoner than sickle cell nephropathy.[7] Fary ka *et al.* had reported a prevalence of Autosomal Dominant Polycystic Kidney Disease (ADPKD) during ten years of study as 1 in 250 patients in a teaching hospital in Dakar, Senegal; the mean annual incidence rate been 15.6% in that study. Reports from Nigeria indicate a prevalence of 8% in Ilorin, among 986 patients seen over a 15 year period [8] and 6.5% in Benin City among 982 patients seen over a 6 year period.[9]

The index patient presented with abdominal pain, fever and episodic haematuria. These are common presentation of patients with ADPKD. The abdominal pain in this patient was dull and continous suggesting that renal enlargement and structural distortion may be responsible for this. Episodes of acute renal pain are seen frequently and causes include cyst haemorrhage, infection, stone and rarely tumor.[1] Fever in this patient was suggestive of urinary tract infection (UTI), which is common in ADPKD. The UTI can manifest with cystitis, acute pyelonephritis, cyst infection, and perinephric abscess. Visible haematuria may be the initial presenting symptom and occurs in up to 40% of ADPKD patients over the course of the disease. Many have recurrent episodes. Differential diagnosis include cyst haemorrhage, stone, infection, and tumor. In most patients, cyst haemorrhage is self limited, resolving within 2-7 days.

On examination, the index patient was found with ballotable kidneys, hypertension and uraemic encephalopathy.

Ballotable kidneys are evidence of renal enlargement. Renal enlargement increase with age, and eventually occurs in 100% of patients with ADPKD. The severity of the structural abnormality correlates with the manifestation of ADPKD such as pain, haematuria, hypertension and renal impairment.[10] Massive enlargement can lead to compression of local structures like inferior vena cava. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study has shown that total kidney volume and cyst volumes increased exponentially.[11] Rates of growth were relatively constant, averaging 5.3% per year, but highly variable from patient to patient. Baseline total kidney volume predicted the subsequent rate of increase in renal volume and decline in GFR.[11] Hypertension is a relatively early finding in ADPKD, a major clinical manifestation and predictor of outcome; with an average onset at 30 years of age.[12] Several factors contribute to the development of hypertension in ADPKD including increased activity of the local intra renal renin-angiotensin system secondary to renal ischemia as a result of expanding cysts, disruption of polycystin function, increased sympathetic nerve activity and plasma endothelin-1 levels and insulin resistance. In most patient, renal function is maintained within the normal range, despite relentless growth of cysts, until the fourth to sixth decade of life. The index patient is in the 5th decade of her life. By the time renal function starts declining, the kidneys usually are greatly enlarged and distorted with little recognizable parenchyma on imaging studies. Several mechanisms account for renal function decline. The CRISP study[13] has confirmed that kidney and cyst volumes are the strongest predictors of renal function decline. The CRISP study also found out that renal blood flow (or vascular resistance) is an independent predictor.[1, 14]

Other renal manifestations of ADPKD include functional manifestation (concentrating defect, reduced renal blood flow), urinary tract infection and nephrolithiasis. Others are hypertension-related complications like heart failure, cerebrovascular accident, arteriolosclerosis, glomerulosclerosis and peripheral vascular disease.

Extrarenal manifestations include

1. Polycystic liver disease: Most common extra-renal manifestation, suspected when there are four or more cysts in hepatic parenchyma with resultant hepatomegally. However there is preservation of hepatic architecture and normal liver function. (as found in this index patient) .
2. Intracranial aneurysms- occur in about 8% of patients with ADPKD. Most are asymptomatic. Can result in cranial nerve palsies, seizure and sub-arachnoid bleed
3. Other vascular abnormalities such as thoracic aortic and cervicocephalic arterial dissections, coronary artery aneurysms, retinal artery and vein occlusions.
4. Valvular heard disease and other cardiac manifestation: These include mitral valve prolapse, mitral regurgitation, tricuspid regurgitation, tricuspid prolapse), pericardial effusion, vascular abnormalities.
5. Other associated conditions: Cysts in pancrease, seminal vesicles, epididymis, prostate and arachnoid

membrane. Sperm abnormalities with defective motility, diverticula in spinal meninges, colon and duodenum.

Diagnosis of ADPKD in this patient was based on renal ultrasound findings. Diagnosis of ADPKD is based on imaging studies with genetic testing only when a precise diagnosis is needed and the results of imaging are indeterminate. Renal ultrasound is commonly used for pre-symptomatic testing because of cost and safety. It also very high positive predictive value of 99% to 100%.[1] Revised unified criteria have been proposed to improve the diagnostic performance of the ultrasound in ADPKD. In families of unknown genotype, the presence of three or more (unilateral or bilateral) renal cysts is sufficient for establishing the diagnosis of at-risk individuals aged 15 to 39 years, two or more cysts in each kidney is sufficient for individuals aged 40 to 59 years, and four or more cysts in each kidney is required for individuals ≥60 years.[15] Conversely, an ultrasound finding of normal kidneys or one renal cyst in at-risk individuals aged ≥ 40 years is sufficient to exclude the disease. The inaccuracy of ultrasound in detecting small cysts or small changes in renal volume may pave way for the use of either CT-scan or MRI.[16] Genetic testing are by linkage analysis or by mutation analysis; both methods having limitations which makes feasibility difficult and pathogenicity of some genetic changes difficult to prove. However, molecular testing by direct DNA sequencing is now informative in about 90% of patients.

Acquired disorders that need to be differentiated from ADPKD include multiple benign simple cysts, localized renal cystic disease, acquired renal cystic disease, medullary sponge kidney and bilateral parapelvic cysts

Current treatment of ADPKD is directed towards its renal and extrarenal complications in an effort to limit morbidity and mortality.[1] Therapeutic include control of hypertension, dietary protein restriction, treatment of co-morbidity, cyst drainage, renal replacement therapy (dialysis or renal transplantation).[16] As the index patient presented with life-threatening complications like anaemia and ureamia, the first line of treatment was to renal replacement therapy with haemodialysis and intradialysis transfusion of blood. Hypertension can be effectively controlled by the use of ACE inhibitors or angiotensin II receptor blockers. Adequate control of hypertension can hinder disease progression with regard to renal volume, proteinuria, cardiovascular complications, and progression to end-stage renal disease. [17] The hypertension in the index patient was effectively controlled with an ACE-inhibitor-containing regimen. There was subsequent improvement in ureamia and proteinuria. In the index patient, the haematuria resolved with treatment of UTI, rehydration and bed rest. In some cases, persistent bleeding may need percutaneous arterial embolization or even nephrectomy.

Other approaches include inhibition of cyst development using vasopressin receptor antagonists like Tolvaptan and potassium sparing diuretics like Amiloride, reduction in cystic fluid secretion by with caffeine restriction and somatostatin analogues.[16] Tolvaptan is an orally active small molecule vasopressin V2 receptor

antagonist which is effective in the treatment of hypervolaemic or euvolaemic hyponatraemia and congestive heart failure. The rationale for its use in ADPKD comes from work showing that arginine vasopressin is a major stimulus for cAMP production in the collecting ducts.[16] Preclinical experiments demonstrated that vasopressin V2 receptor antagonists (OPC-31260 and tolvaptan) consistently inhibited cystogenesis by reducing renal cAMP levels in *pcy* mice, PCK rats and *Pkd2*$^{WS25/-}$ mice' These encouraging findings have translated to clinical trials under the Tolvaptan Efficacy and Safety in Management of PKD and Outcomes (TEMPO) programme.

Surgical approaches include percutaneous aspiration of cyst to relieve intractable pain and discomfort caused by the enlarging cysts and unilateral or bilateral nephrectomy for growing cysts which increase to enormous proportions over time and may lead to chronic pain, chronic haematuria, recurrent urinary tract infections, abdominal hernias and marked fatigue and.[18] Others are laproscopic renal denervation and nephropexy; and transcatheter arterial embolization for massive ADPKD with haemorrhage.[16]

Newer issues and therapies on ADPKD

1. Emerging reports points to some similarities between ADPKD and solid tumors at microscopic and molecular level.[2] This might suggest ways in which therapies developed for one disease might be applied to the other. This is of particular value for ADPKD, for which few therapeutic options are available.
2. Methylprednisolone has been found to decrease the extent of renal enlargement and renal interstitial fibrosis in rats and mice with relatively severe forms of APKD.[19]
3. Previous studies found that the mTOR pathway is upregulated in ADPKD, possibly due to loss of tonic inhibition on mTOR from a tuberin-polycystin-1 complex.[20] Sirolimus (rapamycin) an mTOR inhibitor was found to inhibit cyst formation and decrease polycystic kidney size in several animal models.[20] Sirolimus and Everolimus (another mTOR inhibitor) have undergone clinical trials reporting no significant benefits of either drug on total kidney volume or GFR .[21-23] However, a study among 55 participants with eGFR 40–80 ml min^{-1} 1.73 m^{-2} showed that a higher rapamycin dose (trough concentration ∼6–8 μg l^{-1}) and selection of *PKD1* patients was associated with therapeutic benefit with respect to changes in TKV and eGFR.[24]
4. Src Inhibitors: The Src family of non-receptor tyrosine kinases may contribute to cell proliferation in ADPKD. Bosutinib (SKI-606), a Src/Abl tyrosine kinase inhibitor, was found to suppress kidney cyst formation in the *bpk* and PCK rodent models by suppressing EGF receptor activation and consequent B-Raf/ERK signaling.[25] A phase 2 clinical trial is been conducted to determine the efficacy of Src inhibitors in patients with ADPKD.
5. Triptolide: This is a natural compound derived from *Tripterygium wilfordii*, a traditional Chinese medicine.[26] It was found to restore cytosolic Ca^{2+} release in *Pkd1* null cells by acting as a PC2

agonist. Its use in ADPKD is still under investigation in clinical trials

6. Sorafenib is a non-selective Raf inhibitor that inhibits the proliferation of various human cancer cell lines. Sorafenib is postulated to be an effective treatment in ADPKD since B-Raf plays a critical role in cAMP-dependent activation of ERK in cystic epithelia.[27]
7. Other therapies undergoing different stages of clinical trials include R-roscovitine, a cyclin dependent kinase (CDK) inhibitor that has been shown to inhibit cell cycle progression, proliferation and apoptosis in the *jck* and *cpk* mouse models of PKD;[28] Histone deacetylases (HDACs) inhibitors, which induce cell cycle arrest and apoptosis in tumour cells[29] and cystic fibrosis transmembrane regulator (CFTR) channel inhibitors found to inhibit cyst formation and enlargement in MDCK cyst models and in *Pkd1* mice.[30] Metformin, Glucosylceramide inhibitors, Thiazolidinediones, Curcumin, Gingkolide B, Calcimimetics, Purinergic receptor inhibitors, pyrimethamine and leflunomide are all promising agents at different stages of clinical trials. [31]

CONCLUSION

This is a clinical review of ADPKD using a report of a 49 year old woman who presented with clinical and radiologic features in keeping with the disease. It is a cause of end-stage renal failure in Nigeria. She was admitted and managed for end-stage renal disease secondary to ADPKD. She was treated for UTI, blood pressure control, renal replacement therapy and protein restriction. She made remarkable improvement and was discharged after thirteen days. Six of her relatives and including children were screened for cysts in kidneys. One of the first degree relatives aged 39 years was found with multiple cysts in the both kidney and had been on follow up visit. Cornerstone of diagnosis is radiologic while current treatment of ADPKD is directed towards its renal and extra-renal complications. The identification of *PKD1* and *PKD2* has caused rapid progress in the study of the molecular mechanisms underlying pathogenesis of the disease. This has resulted in a paradigm shift in therapeutics. The result of Tempo 3/4 study gave rise to a major therapeutic shift in ADPKD treatment.[32] With a good number of drugs on clinical trials, it is hoped that many drugs will be made available to suit different patients, while the potential for adverse drug reaction is anticipated. Futhermore, since ADPKD is a genetic disease, it is anticipated that careful risk stratification based on genotype, phenotype, imaging and possibly biomarkers can guide therapy in the future.

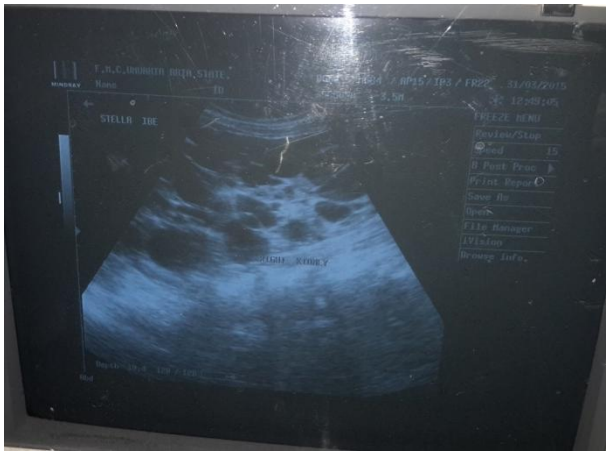

Fig. 1 showing enlarged right kidney with multiple cysts.

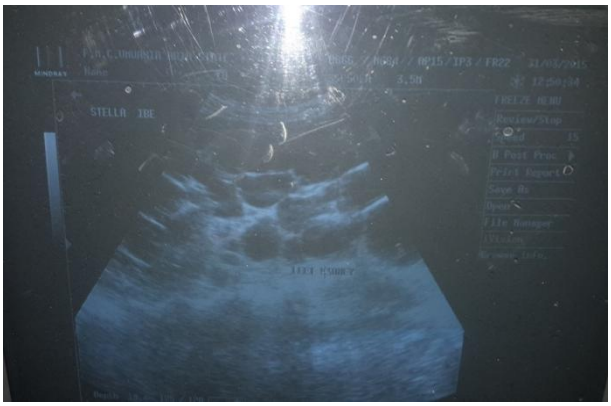

Fig. 2 showing enlarged left kidney with multiple cysts.

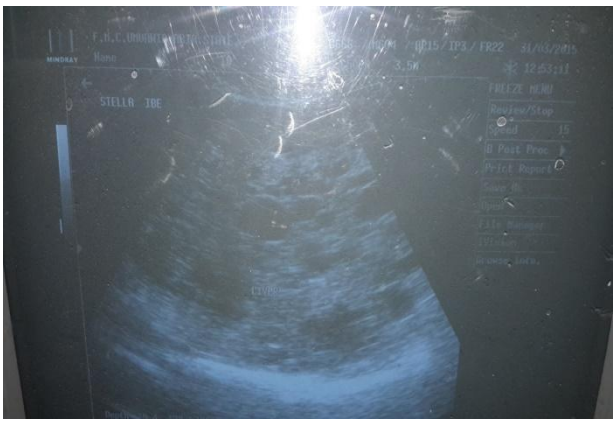

Fig. 3 showing enlarged liver with multiple cysts.

Table 1: Showing the result of some laboratory investigations.

Variable	**Result**	**Reference range**
Serum creatinine (mg/dL)	7.6	0.5-1.5
Serum urea (mg/dL)	215	10-45
Bicarbonate (mmol/L)	9	21-35
Potassium (mmol/L)	5.8	3.5-5.5
Sodium (mmol/l)	138	135-145
White blood cell(/µL)	13 x 10^3	4- 11 x 10^3
Haemoglobin (g/dL)	6.5	10.5-13.5
Platelets	240 x 10^3	150-400 x 10^3
Fasting blood sugar (mg/dl)	81	50-126
Total cholesterol	312	<200
HDL-C (mg/dl)	59	>50
LDL-C (mg/dl)	222	<190
Triglyceride (mg/dl)	193	<150
Serum calcium	6.9	
Serum phosphate	4.2	
Serum albumin	3.2	2.5-4.0
Alanine aminotransferase(iu/l)	16	3-20
Aspartate aminotransferase(iu/l)	11	3-15
Alkaline phosphatase (iu/l)	67	25-92
Protein: creatinine ratio (mg/g)	1,350	<20
Viral screens- Hepatitis B, C and HIV screening were all negative		

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