

**Original Article**

A Study of the spectrum of Urinary Tract infections in patients with Adult Polycystic Kidney Disease – An old problem with a better outcome

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Abstract

Background: Autosomal Dominant Polycystic kidney disease (ADPKD) is the most common hereditary cause of End stage renal disease (ESRD). Urinary tract Infections (UTI) are common in these patients and include a spectrum of both Lower tract and upper tract UTI.

Methods: This retrospective study which included patients of ADPKD who manifested UTI between June 2012 to May 2017. Clinical, Laboratory, imaging and microbiological data was analyzed. Few patients had more than one episode of UTI and there by the total number of UTI episodes were 52. Out of the 58 episodes of UTI, Lower tract UTI and Upper tract UTIs were 13 and 45 episodes. Among the total 45 episodes of upper UTI, 17 were Acute Pyelonephritis and 28 were Cyst infections. 40 % of UTI episodes necessitated Hospitalization.

Conclusions: Cyst infection is the most common form of UTI followed by acute pyelonephritis and Lower tract UTI. Majority of the UTI episodes were caused by *E.coli*. Around 40 % of patients with UTI mandated hospitalization but no episode of death attributable to UTI was noted.

Keywords: Autosomal dominant polycystic kidney disease (ADPKD), Urinary Tract infection (UTI), Acute Pyelonephritis, Cyst infection, Extra renal manifestations.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disorder and it is credited as the commonest hereditary disorder causing End Stage Renal Disorder (ESRD)¹. It has an incidence of around 1 in 500 to 1 in 1,000². In this condition there would be progressive formation of multiple fluid laden

cysts in the renal parenchyma. ADPKD essentially involves adults and is the consequence of mutations in the PKD1 or PKD2 genes, which encode the proteins polycystin-1 and polycystin-2, respectively. By any account, at least 50 % of individuals with ADPKD progress to ESRD usually by sixth decade of life³.

Patients of ADPKD usually seek medical

attention in view of enlarged abdomen, haematuria, infected renal cysts and pain abdomen. Cysts can occur in multiple Sub diaphragmatic organs with Kidney and Liver being the most common sites of cyst formation. Cysts are linked with various attendant complications Viz bleeding into cyst, cyst infection and obstruction. Obstruction due to cyst enlargement is particularly Concertful in Liver⁴. Infections are an important cause of morbidity and mortality in ADPKD patients^{5,6}. Urinary tract infections (UTI) and especially Cyst infections constitute important events in the clinical course of ADPKD patients and they can be at times be recurrent. The current study is intended to study the clinical profile, Microbiology and outcome of UTI in patients with ADPKD.

Material and Methods

This is a retrospective study which included ADPKD patients who experienced either one or more episodes of UTI. The records of such patients between June 2012 to May 2017 were analysed. The inclusion criteria included ADPKD patients who experienced one or more episodes of UTI. Patients who were diagnosed to have acquired cystic kidney disease were excluded. A diagnosis of lower tract UTI was empirically made when patient presented with new onset dysuria and with microscopic pyuria. A diagnosis of Acute pyelonephritis was made when a patient presents with dysuria, flank pain, fever and microscopic or gross pyuria. A diagnosis of Cyst infection was made when the combination of fever, new onset tender nodular areas over the abdomen and C-Reactive protein level of more than 5 mg/dl.

Data regarding Clinical profile, laboratory parameters, imaging studies and Microbiological investigations, Antimicrobial regimen and the response to treatment was recorded and analysed. Urine culture and US Scan abdomen was performed in every patient while Blood Culture was performed in select patients in whom there is suspicion of Upper tract infection or if there is

undue delay in response despite administering appropriate antibiotics as per urine microbiology reports. CT scan Abdomen was performed when UTI does not improve at expected pace, to rule out obstruction due to Nephrolithiasis, when there is a suspicion of perinephric abscess or when the patient presents with a combination of UTI and acute abdomen. Further, the basic laboratory investigations (Renal Function tests, Liver Function Tests, Complete blood count) were performed. Detailed analysis of the Microbiological investigations to incorporate the Microbiological spectrum and antibiotic sensitivity pattern was carried out. IBM SPSS version 22 was used for statistical analysis. Descriptive analysis was carried out by the mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Data was also represented using appropriate diagrams.

Results

This retrospective study included 94 patients of ADPKD during the five year study period (June 2012 to May 2017). 55 Were males and 39 were females. Family History of ADPKD was evident in 88 cases (93.6%). Out of the total 94 patients of ADPKD, 45 patients had UTIs. Among these 45 patients who manifested one or more episodes of UTI, 29 were females (64.5%). Few patients had more than one episode of UTI and there by the total number of UTI episodes were 52. Hypertension was noted in 61 of the total cases (64.8%). Out of the 58 episodes of UTI, Lower tract UTI and Upper tract UTIs were 13 and 45 episodes. Among the total 45 episodes of upper UTI, 17 were Acute Pyelonephritis and 28 were Cyst infections. The symptomatology at the time of presentation was mentioned in Table 1. 29 of the 45 patients with UTI had Hypertension (64.4%). 38 patients had liver cysts (84.4%), while 9 patients had Mitral valve disease as either MVP or mild Mitral Regurgitation (20%). None of the patient had Aortic valve disease. Further none of the patient were screened for Intracranial

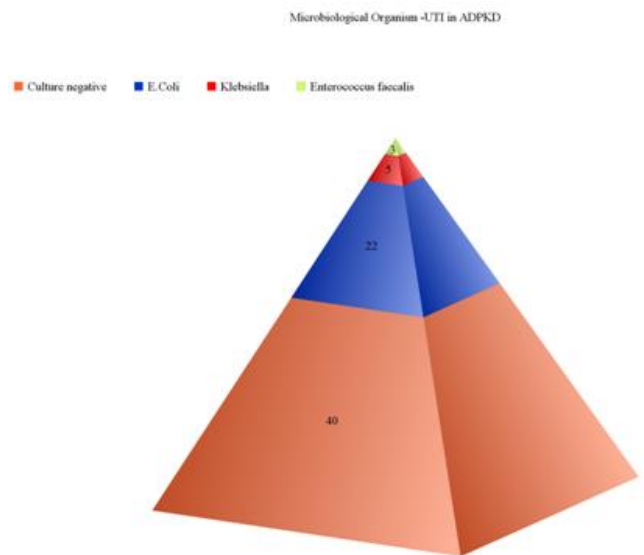
aneurysms as there was negative family of either Cerebral aneurysms or sudden death in any of the family members of the study subjects.

Nephrolithiasis was noted in 12 patients of those presented with UTI (26.7%) and in 2 patients obstruction was evident due to ureteric calculi, which mandated Lithotriptic destoning.

All patients were started on empirical antibiotic regimen consisting of one or more antibiotics, out of which one antibiotic would be a fluoroquinolone antibiotic with good cyst penetration capability (either Ciprofloxacin or Levofloaxacin). Antibiotic therapy was modulated basing on the culture reports. All episodes of UTI included in the study recovered and no deaths were noted.

Table 1: Clinical Presentations in Patients of ADPKD with UTI

S.No	Clinical Symptom	Percentage
1.	Dysuria	94 %
2.	Flank Pain	42 %
3.	Haematuria	27%
4.	Fever	82 %
5.	New onset abdominal Painful nodule	38 %
6.	Vomiting and Nausea	64 %
7.	Diarrhoea	44 %

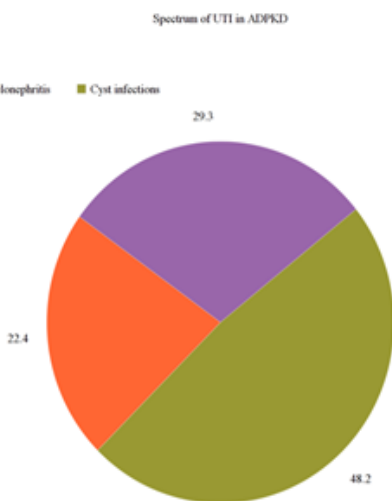


Discussion

UTI which constitute a spectrum with regard to their anatomical location and severity are very common in ADPKD and can present in 30-50 % of ADPKD patients in their life time⁷.UTI is more common in females akin to UTI in the general population⁸.UTI in ADPKD can present as both Lower tract UTI and Upper tract UTI. As the name implies Lower tract UTI indicates Cystitis while the two major types of Upper tract UTI are Acute Pyelonephritis and Cyst infection. Majority of the infections are ascending in nature and the major predisposing factor for UTI in ADPKD being structurally abnormal kidneys and Nephrolithiasis. In the current study, 47.9% of the study population had experienced one or more episodes of UTI. Among those patients who had UTI, 64.5% were females, though males have outnumbered females with respect to the total number of ADPKD patients (those with UTI and without UTI) whose files were analysed in the study period. This denotes the clear cut preponderance of UTI in ADPKD woman similar to UTI occurring in general population.

Family History is usually present in majority of the patients though a typical family history might be absent in up to 25 % of patients⁹. In this study, 93.6% of total ADPKD patients reported positive family History.

Hypertension is common in ADPKD like any



other cause of Chronic kidney disease. Hypertension is noted in around 50-70 % of ADPKD patients and it might manifest even before the onset of decline of renal function¹⁰. The average ages of diagnosis of ADPKD is 27 while the age of detecting Hypertension in ADPKD is around 31 years¹¹. In the current study, Hypertension is noted in 61 % of the study subjects, implying that the incidence of Hypertension is uniform across the various geographical regions.

In ADPKD, both lower and Upper tract UTIs are common and contribute to mortality and morbidity⁵. However, there is paucity of data regarding the distribution of various forms of UTI in ADPKD patients with the exception of Cyst infections. In the current study, Out of the 58 episodes of UTI, 22.4 % (13 episodes) were of lower tract UTI and 77.58 % (45 episodes) were of Upper tract UTI. Among the upper tract UTIs, approximately one third were Acute Pyelonephritis episodes and two thirds were Cyst infections. Pyelonephritis and cyst infections contributed for 29.3 % (17 episodes) and 48.2 % (28 episodes) of total UTI episodes. Out of the total 58 episodes of UTI, in 23 episodes patients necessitated admission in view of severe nature of UTI. This indicates that almost 40 % of episodes of UTI in ADPKD cases required hospitalization. The reasons for hospitalization included persistent high grade fever, inability to maintain optimal hydration, presence of obstruction and the impending multiorgan nature of Sepsis syndrome. This rate of hospitalization is higher than the need for hospitalization in general population with acute pyelonephritis and this would portend the complex nature of UTI in ADPKD patients.

The incidence of Cyst infection in ADPKD is reported as around 0.01 episode per patient with an estimated microbiological evidence in 75 % of cyst infections. *Escherichia coli* was reported to be responsible for cyst infection in around three fourths of such cyst infections. 10 % of hospitalizations in ADPKD patients are accountable for cyst infection. The diagnosis of

cyst infection constitutes a diagnostic challenge and is based on clinical features such as features of sepsis on the back drop of new onset tender nodules over the abdomen. Definitive diagnosis utilizing cyst aspiration of pus and the microbiological testing of cyst fluid is not always practically feasible. The inability of CT and MR imaging to differentiate between Cyst infection and Cyst haemorrhage adds to the complexity of diagnosis of cyst infection⁴. Renal cyst infection in ADPKD can be at times be a challenging task as the presentations are protean in nature and can even present like a mass lesion mimicking a malignant lesion¹².

Francois et al described the criteria of Cyst infection as the combination of four parameters Viz. fever, new onset tender nodular areas over the abdomen and C-Reactive protein level of more than 5 mg/dl and absence of intra cystic density of more than 25 Hounsfield units on CT imaging of kidneys¹³.

In the current study, Cyst infections were the most common form of UTI by accounting to 48.2 % of total UTI episodes. Further cyst infections contributed for almost two thirds of upper tract UTIs. Further out of 28 cases of Cyst infections, 18 cases necessitated hospitalization (64.28 % of Cyst infection cases).

Urine culture is usually sterile in Cyst infections as Cysts larger than 2 Cm in size usually gets detached and establish no communication with the kidney tubule¹⁴. Therefore either Blood culture or microbiological study of the fluid aspirated from the cyst in question would result in bacteriological yield. It is prudent to note that demonstration of microbiological positivity in cyst aspirate, though considered gold standard is not always practically feasible¹⁵.

In the current study, Urine culture was positive in 80 % cases (10 episodes) of Lower tract UTI, 88.2 % cases (15 episodes of UTI) of acute pyelonephritis and in only 15 % cases (5 episodes of UTI) of Cyst infection. Blood culture was positive in none of the cases of lower tract UTI, 17.6% cases of Acute pyelonephritis (3 episodes

of UTI) and in 42.8 % cases (12 episodes of UTI) of Cyst infection. In cases where in urine C&S was positive, E.coli was isolated in 73.3% of cases (22 out of 30 total episodes with Urine Culture positivity), while Klebsiella and Enterococcus faecalis were isolated in 16.6 % (5 episodes of Culture positive UTI) and 10 % of cases (3 episodes of culture positive UTI).

Conventionally Nephrolithiasis is described in around 20 % of individuals with ADPKD and majority of the stones were either Calcium oxalate or uric acid. In the current study, Nephrolithiasis was noted in 12 patients of those presented with UTI (26.7%) And in 2 patients obstruction was evident due to ureteric calculi, which mandated Lithotriptic destoning¹⁵.

Extra renal manifestations are the rule in ADPKD and the major organs involved being Liver, Heart, Brain. Liver cysts are noted in around 80 % of individuals and liver cysts might appear 10 years after the onset of renal cysts¹⁶. Hepatic cysts unlike renal cysts will not impede hepatic functions except when they cause obstruction to the biliary system. 25 % can have cardiac abnormalities and 8 % can have Intra cranial aneurysms¹⁷. In the current study, hepatic cysts were noted in all the individuals of ADPKD who presented with UTI. Mitral valve prolapse was noted in 17 % and mild Mitral Regurgitation was noted in 6% of individuals. None had aortic valve lesions. None of the patients had been screened for intra cranial aneurysms as none of them had family history of neither the Sudden death nor the intra cranial aneurysm.

Infection is considered as an important causes of death in ADPKD patients. Death rate due to infection was more than 30 % prior to 1975 but the rate has declined to around 15 % in the first decade of Twenty First Century^{5,6}. But in the current study, though around 40 % of UTI episodes necessitated Hospitalization, mortality due to Sepsis was documented in none. This could be because of the wide spread awareness about the potential seriousness of UTI and infections in ADPKD and due to our institutional policy of

administering intra venous antibiotics empirically without delay at the first suspicion of UTI in ADPKD patients.

Conclusion

ADPKD is a ciliopathy and an important cause of ESRD globally. Even though ESRD is manifested after fifth decade of life, the course of ADPKD patients is punctured with multiple renal and extra renal complications. One such Renal complication is Urinary Tract infection. In the current study Cyst infection is the most common form of UTI followed by acute pyelonephritis and Lower tract UTI. Majority of the UTI episodes were caused by E.coli. Around 40 % of patients with UTI mandated hospitalization but no episode of death attributable to UTI was noted, indicating the importance of initiation of intravenous antibiotic at the earliest suspicion of UTI in ADPKD patients.

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