BANTAO Journal 2011; 9 (1): 19-22

BJ
BANTAO Journal

Original article

Bacteriological Findings and Treatment of Urinary Tract Infections in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Introduction. Urinary tract infections are common in patients with autosomal dominant polycystic kidney disease (ADPKD) but the exact prevalence of upper urinary tract infection is not well established. The aim of this study was to evaluate the bacteriological findings and the frequency of urinary tract infections in autosomal dominant polycystic kidney disease and their impact on renal function.
Methods. One hundred eighty patients with autosomal dominant polycystic kidney disease were studied from 2003 to 2008. Subjects were considered as having urinary tract infections if they had one or more episodes of urinary infection. The antibiotic therapy has been adapted according to the bacteriological findings.
Results. Urinary tract infections were observed in 60% of our patients (108 patients), and were more frequent in women than in men. The infections were typically caused by gram negative organisms. Blood culture was positive in 10%, while urine culture was negative in 40% of cases. The episodes of isolated cyst infections (negative urine culture and absence of white blood cell casts in urinary sediment) were more frequent than those of acute or chronic pyelonephritis (urinary sediment was positive for white blood cell casts).
Conclusion. We conclude that urinary tract infections are frequent in our patients with ADPKD. Distinguishing between cyst infection and acute or chronic pyelonephritis is often a challenge, and the diagnosis relies mainly on clinical and bacteriological findings.

Keywords: autosomal dominant polycystic kidney disease, bacteriological findings, cyst infection, radiological findings, urinary tract infections.

Introduction

Urinary tract infections are common in patients with autosomal dominant polycystic kidney disease (ADPKD) and have an influence on renal function [1-3]. The exact prevalence of upper urinary tract infection has not been well evaluated. Causal organisms generally reach the kidneys by the ascending route. Patients may present infections of the bladder, perinephric tissue, cysts and renal interstitium [1]. Upper urinary tract infections are mostly caused by gram-negative bacteria commonly responsible for lower urinary tract infections. Occasionally, infection is caused by gram-positive and anaerobic bacteria. Kidney infection is potentially severe since it may be complicated by septic shock or perinephric abscess. There are also doubts about the adverse effects of urinary tract infection on the progression to renal failure in ADPKD [4,5]. The aim of this study was to evaluate the frequency of urinary tract infections in ADPKD, bacteriological findings and their impact on renal function.

Material and Methods

One hundred eighty patients with ADPKD were studied from 2003 to 2008. The diagnosis for ADPKD was based on the criteria established by Ravine *et al.* in 1994 [6] then modified by Pei *et al.* [7]: presence of polycystic kidney and a typical family history or, in the absence of family history, presence of three or more (unilateral or bilateral) renal cysts for individuals aged between 15 to 39 years, two or more cysts in each kidney for individuals aged 40 to 59 years, and four or more cysts in each kidney for individuals aged >60 years. Subjects were considered as having urinary tract infections if they had had one or more episodes of urinary tract infections. The diagnosis of cyst infections and radiological evaluation were based on the following:

- Cyst infection was considered as likely in the presence of all of the following features: Fever (tempe-

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rature >38.5°C for >3 d), abdominal pain (particularly a palpable area of renal or liver tenderness), increased C-reactive protein (CRP >50 mg/L), and absence of any significant recent intracystic bleeding (based on the results of an abdominal computed tomography [CT] scan) or other causes of fever.

- Kidney and liver ultrasound data were considered positive when debris with a thick wall and/or a distal acoustic enhancement was detected in at least one cyst.
- Kidney and liver CT scan and magnetic resonance imaging (MRI) data were considered positive when enhanced wall thickening and/or perilesional inflammation was detected in at least one cyst.
- Efficacy of antibiotic treatment and infection eradication were defined by the disappearance of fever, normalization of CRP levels, and at least two negative blood and/or urine cultures [8].

The antibiotic therapy has been adapted according to the bacteriological findings. Oral administration of antibiotics with good intracystic penetration such as trimethoprim (baktrim) or preferably a fluoroquinolone such as ciprofloxacin, has been selected for long term treatment in patients with more than three episodes of urinary tract infections in last six months. Treated patients were compared with patients without urinary tract infections (untreated patients). We used trimethoprim 480 mg 1 cpr/day alternate weeks for three months, discontinued for three months, again alternate weeks for three months and so on. Results are reported as mean±SD. P values ≤ 0.05 were considered statistically significant.

Results

Urinary tract infections were observed in 60% of our ADPKD patients (108 patients) (mean age 45.4±6.2 years, range 18-65 years), and were more frequent in women than in men (Table 1). 47 patients had cyst infections, 41 patients had acute pyelonephritis and 20 patients had bladder infection. Microbiological data were available in 75% of patients with episodes of urinary tract infections. The infections were typically caused by gram negative organisms (Figure 1). The blood culture was positive in 10% of patients, while urine culture was negative in 40%. The episodes of isolated cyst infections (negative urine culture and absence of white blood cell casts in urinary sediment) were more frequent than those of acute or chronic pyelonephritis (urinary sediment was positive for white blood cell casts). For all patients the ultrasound scan examination was performed. In 18 patients the CT scan revealed the heterogeneous contents and irregularly thickened walls of infected cysts. MRI showed cyst infection in 5 more cases in which no infection was determined with CT scan. C reactive protein was measured in almost of patients and found very high in 50 % of patients with cyst infections and in all of them with parenchymal infection.

Table 1. Demographic data of patients

	Patients with UTI (108 patients)	**Patients without UTI (72 patients)**	**P value**
Age	45.4±6.2 years	47.2±7.6. years	NS
Sex Females/Males	60/48	32/40	NS
Renal function GFR≥60 ml/min/ GFR<60ml/min	67/41	42/30	<0.05
BMI (kg/m^2)	28.2±4.5	21.0±3.9	<0.05
Gross hematuria	65(56%)	36(43%)	NS
Mean age	41.4±4.5 years	42.7±3.6 years	
Kidney stones	70(64%)	46(63%)	NS

GFR-glomerular filtration rate, BMI-body mass index, UTI-urinary tract infections, NS-not significant

The response to antibiotics has not been uniform. In some patients, the infection was rapidly controlled, while in 35% of patients fever was still present after 5 days of treatment. Those with cyst infections were treated with antibiotics with good intracystic penetration, like fluorquinolones, while those with acute pyelonephritis were treated with antibiotics with good parenchymal concentration like cephalosporines of second or third generation. Those with episodes of cyst infections were treated with trimethoprim for three to six months for prevention of recurrent cyst infections.

In patients with a severe renal infection, associated with septicemia parenteral administration of a fluoroquinolone or a third-generation cephalosporin was used as initial therapy.

Treated patients with urinary disinfectants had a significantly lower frequency of urinary infection (p<0.001) and hematuria (p<0.001) after one year of treatment than untreated patients. Moreover, treated patients demonstrated a slope of serum creatinine of 0.0007 vs. 0.0148 of untreated patients (p<0.001) (Figure 2).

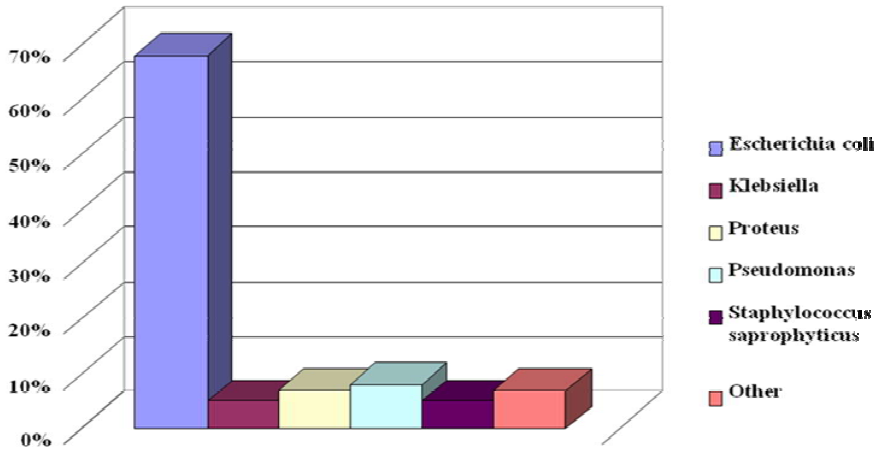

Fig. 1. The frequency of microbial agents for urinary infections

Discussion

Approximately 30 to 50 percent of patients with autosomal dominant polycystic kidney disease (ADPKD) will have a urinary tract infection during their lifetime [2,9]. Cyst infections that need hospitalization occur much less frequently, approximately in 9% of patients [8]. Patients may experience symptoms from cyst infections, cyst hemorrhage, or pain from ruptured or expanding cysts. Urinary tract infections are frequent in our ADPKD patients being more frequent in women than in men (female to male ratio 2.1/1.5) as reported in literature [8]. The finding of E. coli on more than 60% of our cases suggests an ascending mechanism for cyst infection, at least in the case of a positive urine culture. The differentiation between parenchymal and cyst infection is not always easy [10]. The former is evidenced by a positive urine culture and prompt response to antibiotic therapy. The latter is characterized by the development of discrete, new palpable area(s) of renal tenderness, a quite often negative urine culture (as infected cysts may not communicate with the pelvis), a very high proportion of positive blood cultures, and apparent refractoriness to antibiotic therapy. In difficult cases,

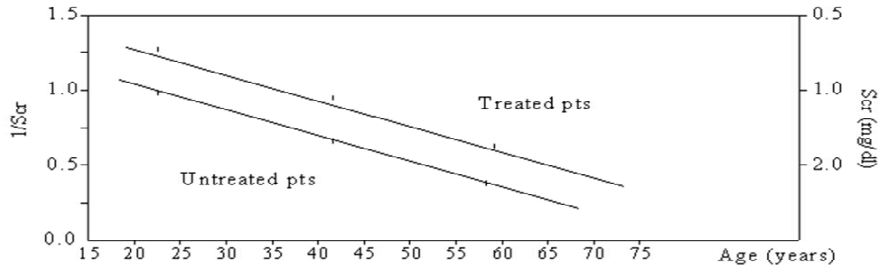

Fig. 2. Slope of the reciprocal of serum creatinine of treated and untreated patients

imaging techniques such ultrasonography or, more often, CT scan may provide valuable information [10]. We used CT scan and MRI as diagnostic tools in some difficult cases and the results were very helpful for diagnosing infected cysts. While Rule *et al*. [11] reported that history of urinary tract infections was identified as a prognostic factor for a decline in measured glomerular filtration rate; our study showed that the right treatment of urinary tract infections decreased their frequency and has beneficial role in the rate of progression to renal failure. The refractory nature of cyst infection has been shown to be largely due to poor penetration of commonly used antibiotics into cyst fluid [12]. A major route for antibiotic penetration into the cyst is indeed diffusion across the cyst

wall, a property dependent on lipid solubility. Lipophilic antibiotics (such as trimethoprim, fluoroquinolones, chloramphenicol, and metronidazole) rapidly achieve high intracystic concentrations. Fluoroquinolones and third-generation cephalosporins remain the standard treatment for cyst infections in patients with ADPKD and we used them in 35% of the patients with urinary tract infections included in this study. The optimal duration of antibiotic administration is unclear. There is no evidence that giving antibiotics for more than 3 weeks has significant advantage in common cases of parenchyma infection [12]. Based in our experience, we recommend a 12-week (three months) course in proven or suspected cyst infection. If the infection recurs after withdrawal of antibiotics, treatment should be reinstituted and continued for other 12 weeks.

Conclusion

We conclude that urinary tract infections are frequent in our ADPKD patients. The infections were typically caused by gram-negative organisms Distinguishing between cyst infection and acute or chronic pyelonephritis is often a challenge, and the diagnosis relies mainly on clinical and bacteriological findings. The long course treatment with antibiotics is associated with a better renal function.

Conflict of interest statement. None declared.

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