ORIGINAL ARTICLE

The influence of renal manifestations to the progression of autosomal dominant polycystic kidney disease

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Abstract

Background: Renal stones, urinary tract infections (UTI) and gross hematuria (GH) are the most important renal manifestations of autosomal dominant polycystic kidney disease (ADPKD). They are not only common, but are also frequent cause of morbidity, influencing renal dysfunction. The aim of this study was to evaluate the frequency of these manifestations in our patients with ADPKD and their impact on renal function.

Methods: One hundred eighty ADPKD patients were included in the study. Subjects were studied for the presence of UTI, gross hematuria frequency and responsible factors of nephrolithiasis. Survival times were calculated as the time to renal replacement therapy or time of serum creatinine value up to 10 mg/dl. Kaplan-Meier product-limit survival curves were constructed, and log rank test was used to compare the survival curves.

Results: Kidney stones were present in 76/180 (42% of pts). The stones were composed of urate (47%) calcium oxalate (39%), and other compounds 14%. UTI was observed in 60% (108 patients). Patients treated with urinary disinfectants had a significant lower frequency of urinary infection ($p<0.001$) and hematuria ($p<0.001$) after one year than untreated patients. Gross hematuria was present in 113 patients (63%). In 43 patients hematuria was diagnosed before age 30 (38%), while in 70 patients it was diagnosed after age 30 (62%).

Conclusions: UTI is frequent in our ADPKD patients. The correct treatment of UTI decreases its frequency and has beneficial role in the rate of progression to renal failure in ADPKD patients. Patients with recurrent episodes of gross hematuria may be at risk for more severe renal disease. Hippokratia 2009; 13 (3): 161-164

Key words: autosomal dominant polycystic kidney disease, renal stone, urinary tract infection, gross hematuria

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Nephrolithiasis is an important manifestation of ADPKD, which ranges from 8% to 36% in different studies. It is not only common, but it is also a frequent cause of morbidity and is common in women as in men[1-7]. Half of ADPKD patients are symptomatic and 20% require surgical removal of the stones. Uric acid and calcium stones are the most frequent types of stones in polycystic kidney disease patients. Nevertheless, hyperuricosuria and hypercalciuria do not occur consistently in them[8].

Urinary tract infections are common in patients with ADPKD[9-11]. However, frequent episodes of UTI are less common and are seen more frequently in females than in males. Patients may present infections of the bladder, perinephric tissue, cysts and renal interstitium[9]. There are also doubts about the adverse effects of urinary tract infection on the progression to renal failure in ADPKD[12,13].

Gross hematuria has been commonly reported in ADPKD[14]. It is not only common but it can trigger the diagnosis in 13% to 23% of adult ADPKD subjects[13], influencing renal dysfunction[15,16].

We report our experience about the frequency and the factors responsible of nephrolithiasis, UTI, GH and their impact on the progression of renal failure in ADPKD patients during 10 years.

Patients and Methods

One hundred eighty patients with ADPKD were studied during last 10 years. For anatomic evaluation, the patients underwent renal ultrasonography to determine cyst number, predominant cyst size and stones. A plan abdominal X-ray for some patients was performed.

For metabolic evaluation urinanalysis, urine culture, urinary pH, calcium, oxalate, citrate, uric acid, phosphate, magnesium, creatinine levels in a 24-h urine specimen were performed in all patients. Serum calcium, phosphate, uric acid, magnesium, and creatinine levels were also determined.

Patients with nephrolithiasis were defined as those with calculi within the collecting system of the kidney on ultrasound with or without a clinical history of stones. Criteria for the sonographic diagnosis of calculus included identification of an echogenic focus with posterior acoustic shadowing within the kidney but outside an

identifiable cyst. Calculi associated with cyst walls were not tabulated as calculi.

Subjects were considered as having UTI if there was a history of two or more episodes of UTI. The antibiotic therapy of UTI has been adapted according to urine cultures and oral administration of antibiotics with good intracyst penetration such as cotrimoxazole or preferably a fluoroquinolone such as ciprofloxacin, had been choosen for long term prophylaxis. One hundred eight treated patients were compared with 72 untreated patients. A urinary disinfectant – bactrim 480 mg 1cpr/day alternate weeks for three months, discontinued for three months, again alternate weeks for three months and so on. Another prophylactic treatment alternative except bactrim has been nalidixic acid.

Patients were considered having gross hematuria if there was a history of observing blood macroscopically in the urine and microhematuria if the urinalysis showed up to 5 rbc/hpf.

Statistical analysis. Survival times were calculated as the time of starting renal replacement therapy or the time of serum creatinine value up to 10 mg/dl. Kaplan-Meier product-limit survival curves were constructed, and log rank test was used to compare the survival curves.

Results

Kidney stones were present in 76 of our patients with autosomal dominant polycystic kidney disease (42%), with a mean age of 40±4.2 years (range from 16 to 67 years). Forty six patients with nephrolithiasis (61%) were women, while 30 patients were men (39%). Seventy five of our patients were symptomatic and only two of them (3.6%) required surgical treatment. The stones were composed of urate (47%), calcium oxalate (39%), and other compounds 14% (Figure 1). The calculi were associated with an abnormal low urinary pH (5±0.3) (62%). Of the patients studied, hypocitraturia was found in 43%, hyperuricemia in 28%, hyperoxaluria in 17%, hyperuricosuria in 42%, and hypercalciuria in 12%. In 40% of patients the presence of calculi was associated with a history of urinary tract infections and flank pain.

UTIs were observed in 60% of our ADPKD patients (108 patients), and were more frequent in women than in men (F: M ratio 2.1/1.5). Also, 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 positive for white blood cell casts). In 10 patients the CT scan revealed the heterogeneous contents and irregularly thickened walls of infected cysts. 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).

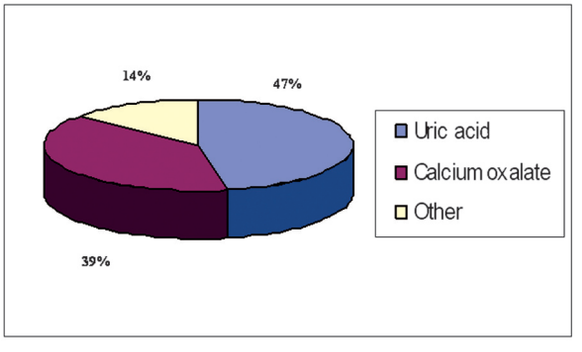

Figure 1: The composition of kindey stones (%).

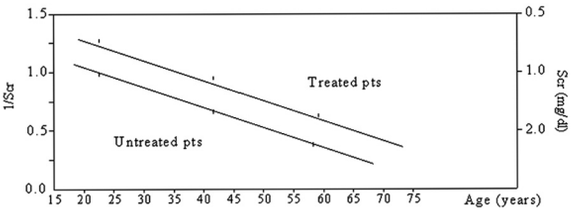

Figure 2: Slope of the reciprocal of serum creatinine of treated and untreated pts.

Gross hematuria was present in 113 patients (63%). Sixty seven patients were females (16 of them underwent nephrectomy), and 46 were males (12 of them underwent nephrectomy). In 39 patients gross hematuria was due to renal cyst rupture into the renal pelvis and in 52 patients renal calculi were the cause of gross hematuria. In 61 patients the gross hematuria was associated with the presence of urinary tract infection. Four patients with gross hematuria proved to have renal malignancy in CT. In 43 patients gross hematuria was diagnosed before age 30 (38%), while in 70 patients it was diagnosed after age 30 (62%). Episodes of gross hematuria before the age of 30 was associated with a worse renal survival compared to those not having such an episode (10-year difference in renal survival; $p < 0.001$) (Figure 3).

The difference in survival of those who had gross hematuria before the age of 30, compared with those who did not have this experience, was significant either for women (Figure 4) or men (Figure 5) (the difference in 9-year renal survival, $p < 0.001$ and 12-year, $p < 0.001$ respectively).

Discussion

Renal stones are a frequent complication of autosomal dominant polycystic kidney disease and are reported to occur in 11% to 34% of patients[1-7]. In our study there were present in 42% of patients, more than the frequency reported in literature. They are not only common, but also a frequent cause of morbidity. Of 76 patients with autosomal dominant polycystic kidney disease and nephrolithiasis, 75% had been symptomatic and 7.6% of them had required some form of surgery. In 40% of patients the presence of calculi was associated with a history of urinary tract infections and flank pain. Torres et al found the frequency of nephrolithiasis equal between men and

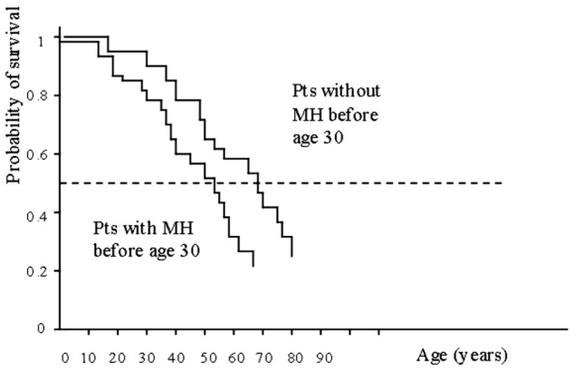

Figure 3: Kidney survial in pts having or not gross hematuria episodes before the age of 30.

women in a population of autosomal dominant polycystic kidney disease patients with normal renal function[8], while in our study nephrolithiasis was more frequent in women. To detect urinary calculi, all patients with ADPKD submitted an ultrasound or direct renal radiography. Since CT is costly, we used it only in some difficult cases. Recently, Nishiura et al have shown that CT for detecting urinary calculi has a sensitivity and specificity respectively 63% and 81%[17].

While urinary excretion of both calcium and uric acid is in the normal range, a decreased urinary excretion of citrate and magnesium, which are powerful inhibitors of crystal formation, is frequently found[8]. Though stones in polycystic kidney disease are composed from uric acid and calcium, hyperuricosuria and hypercalciuria do not occur consistently in polycystic kidney disease patients[8,18]. The presence of low urinary pH, hypocitraturia, hyperuricemia, and hyperuricosuria in our patients reinforce the importance of metabolic factors in the stone disease associated with autosomal dominant polycystic kidney disease as reported and in other studies[19]. The frequency and nature of the stones encountered in these patients have some practical implications. Generous water intake and cranberry juice must be recommended as a general prophylactic measure for every patient with ADPKD and normal renal function.

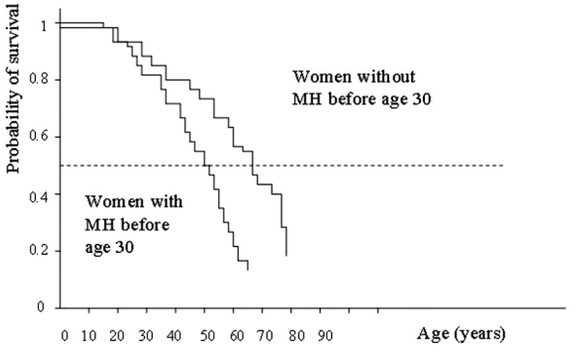

Figure 4: Patient survival (women) in case of gross hematuria or not before the age of 30.

Both anatomic and metabolic factors such as distortion of the renal collecting system, hypocytraturia, hyperuricosuria and hyperuricemia are believed to contribute to stone formation in our patients with ADPKD as reported in the literature. This high frequency of nephrolithiasis (42%) in our patients, may be related to the fact that Albania is in an area of endemic urinary stone disease.

Symptoms of urinary tract infection were the initial manifestation in 3 per cent of men and 42% of women, and occurred at least once in 19% of men and 68% of women with ADPKD studied by Milutinovic et al[2]. UTIs 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. The differentiation between parenchymal and cyst infection is not always easy. 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. In difficult cases, imaging techniques such ultrasonography or, more often, CT may provide valuable information[20].

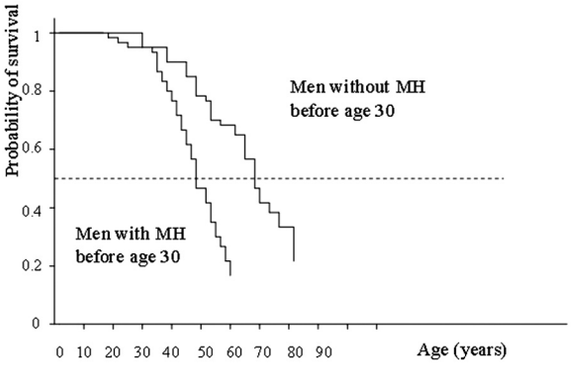

Figure 5: Patient survival (men) in case of gross hematuria or not before the age of 30.

We used as a diagnostic tool the CT in five difficult cases. While Rule et al[21] reported that history of UTIs was identified as a prognostic factor for a decline in measured GFR, our study showed that the correct treatment of UTIs 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[22]. A major route for antibiotic penetration into the cyst is indeed diffusion across the cyst wall, a property dependent on lipid solubility[22]. Lipophilic antibiotics (such as trimethoprim, fluoroquinolones, chloramphenicol, and metronidazole) rapidly achieve high intracystic concentrations[22]. 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[22]. 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.

Gross haematuria is the presenting symptom in 15–20 per cent and occurs at least once in 30–50 per cent of patients with ADPKD[2,15]. Gross hematuria is usually secondary to renal cyst rupture into the renal pelvis. Infection, segmental renal infarction, and passage of renal calculi also cause gross hematuria in ADPKD patients. Its incidence increases with the degree of kidney enlargement. It may follow strenuous physical activity or minor trauma but often occurs spontaneously. If hematuria is recurrent or persists for more than two weeks and the patient has other risk factors associated with the development of renal malignancies, then the possibility of neoplasm should be investigated[23]. Renal malignancies do not occur in a greater frequency in ADPKD patients than they do in the general population[24]. Treatment of hematuria secondary to cyst rupture consists of rest, hydration and analgesics.

In our study the fact that patients who experienced at least one episode of gross hematuria before age 30 had a worse renal survival than patients not having such an episode is interesting (10-year difference in renal survival). These data suggest that patients with recurrent episodes of gross hematuria may be at risk for more severe renal disease since the mean age of the first episode of hematuria occurred on average at 30 years, considerably earlier than renal functional deterioration occurs. Rest is the best management for cyst bleeding. Gross haematuria rarely lasts for more than 7 days[15]. Blood transfusion is rarely required. Very rarely, bleeding may be severe and persistent, notably in dialyzed patients, necessitating uninephrectomy.

We conclude that UTIs are frequent in our ADPKD patients. The correct treatment of UTIs decreases their frequency and has beneficial role in the rate of progression to renal failure in ADPKD patients. Patients with recurrent episodes of gross hematuria may be at risk for more severe renal disease since the mean age of the first episode of hematuria occurred on average at 30 years, considerably earlier than renal functional deterioration occurs. Both anatomic and metabolic factors are believed to contribute to stone formation in our patients with autosomal dominant polycystic kidney disease, as reported in literature.

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