Cent. Eur. J. Med. • 6(4) • 2011 • 497-501
DOI: 10.2478/s11536-011-0043-z

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Central European Journal of **Medicine**

Prevalence of nephrolithiasis in polycystic kidney disease

Research Article

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Received 29 January 2011; Accepted 20 April 2011

Abstract: We aim to define the prevalence of nephrolithiasis, the impact of anatomic and metabolic factors to stone formation and prognosis of patients with autosomal dominant polycystic kidney disease in Albania. We included 200 patients with autosomal dominant polycystic kidney from 2002 to 2009. The patients underwent X-ray, renal ultrasonography. We performed the metabolic evaluation of blood and urine. Survival times were calculated as the time to dialysis, transplantation, or death. Kaplan-Meier product-limit survival curves were constructed. Log rank test was used to compare the survival curves. Nephrolithiasis was present in 116 of our patients with autosomal dominant polycystic kidney disease (58%), with a mean age 46.4±5.7 years. Sixty five patients with kidney stones (56%) were women. The stones were composed primarily of urate (47%) and calcium oxalate (39%), and other compounds 14%. In 40% of patients the presence of stones was associated with a history of urinary tract infections and flank pain. In our study the prevalence of nephrolithiasis is 58%, higher than it reported in literature. Except anatomic and metabolic factors, there are other contributor factors to stone formation in our patients such socioeconomic status of patients, geographic zones and dietary habits.

Keywords: *Autosomal dominant polycystic kidney disease • Gross hematuria • Metabolic factors • Nephrolithiasis • Urinary tract infections*

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited diseases in humans, affecting 4 to 6 million people worldwide, and accounts for end-stage renal disease (ESRD) in 7 to 10% of hemodialysis and renal transplant patients [1]. Nephrolithiasis is an important manifestation of ADPKD, which ranges from 8% to 36% in different studies.

It is a frequent cause of morbidity because of flank pain, hematuria, and urinary tract infections [2-8]. Nephrolithiasis is as common in females as in males and is asymptomatic in 50% of patients [5]. Patients with ADPKD may be predisposed to stone formation because of a structural abnormality secondary to cyst growth, renal tubular stasis, metabolic disorders or a combination of these factors [5,9]. Uric acid and calcium stones are the most frequent types of stones in ADPKD patients. Nevertheless, hyperuricosuria and hypercalciuria do not occur consistently in them [10].

We try to identify the prevalence of nephrolithiasis, the impact of anatomic and metabolic factors to the stone formation and prognosis of patients with ADPKD in Albania.

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Table 1. Demographic data of patients.

	Patients with nephrolithiasis (116 patients)	Patients without nephrolithiasis (84 patients)	*P* value
Age	46.4±5.7 years	49.1±8.9 years	NS
Sex			NS
Females/Males	65/51	38/46	
Area of origin	78/38	31/53	
Rural area/Citizen area			<0.001
Renal function			
GFR≥60 ml/min/GFR<60 ml/min	71/45	54/30	NS
BMI (kg/m^2)	29.4 ± 5.5	21.0 ± 3.9	<0.05
Gross hematuria	65 (56%)	36 (43%)	NS
Mean age	41.2±4.9 years	43.8±3.5 years	
UTI	70 (60%)	38 (45%)	NS

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

2. Material and Methods

In a retrospective observational study we included two hundred patients with ADPKD, who have been followed up regularly in our service from 2002 to 2009. Those patients who did not show up regularly for follow up, were excluded from the study. The diagnosis for ADPKD is done based on criteria established by Ravine et al. in 1994 [11]: the 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 over 60 years old.

All patients underwent renal ultrasound to determine cyst number and predominant cyst size. Patients with nephrolithiasis were defined as those with stones within the collecting system. To diagnose renal stones we used all imaging methods, renal ultrasound (identification of an echogenic focus with posterior acoustic shadowing within the kidney), plain abdominal kidney–ureter–bladder film (KUB) for radiopaque stones, intravenous pyelography (more rarely), which can provide both anatomical and functional information on stones and the urinary tract and non-contrast helical computed tomography (CT) scan in cases when nephrolithiasis was not observed by KUB or renal ultrasound.

Knowing the risk factors, which affect the progression of renal disease such as gender, race, age, renal volume, arterial hypertension, proteinuria, we tried to avoid the role of these factors in the progression of the disease when we chose patients for the study (with stable arterial hypertension, no proteinuria, the kidneys no larger than 14 cm).

Subjects were considered as having UTI if they had had one or more episodes of parenchymal or cyst infections: the presence of fever (temperature > 38.5°C for more than three days), abdominal pain, increased C-reactive protein (CRP > 50 mg/L) [12].

Hematuria, or blood in the urine, was considered to be either gross (visible) or microscopic (as defined by more than three to five red blood cells per high power field when viewed under magnification. For metabolic evaluation urinanalysis, urine culture, urinary pH, calcium, uric acid, citrate, oxalate, magnesium, phosphate, creatinine levels in a 24 hours urine specimen were performed in all patients. Thiazides were withdrawn at least 72 hours before urine collection. Abnormal low pH of the urine was considered fewer than 5.5 [13].

Hypercalciuria was defined as the excretion of urinary calcium in excess of 4 mg/kg of body weight per day or as urinary excretion of more than 250 mg of calcium per day in women or more than 275-300 mg of calcium per day in men, hyperuricosuria as urinary excretion of uric acid greater than 800 mg/day in men and greater than 750 mg per day in women, hypocitraturia as urinary citrate excretion of less than 320 mg per day, hyperoxaluria as urinary oxalate excretion of more than 45 mg per day, and hypomagnesuria as urinary magnesium excretion of less than 70 mg per day as described previously [14]. Serum calcium, uric acid, magnesium, phosphate, and creatinine levels were also determined.

Statistical analysis. Survival times were calculated as the time to dialysis, transplantation, or death, whichever came first. In subjects not reaching ESRD or death, the date of the last serum creatinine value obtained was the cut off time. Kaplan-Meier product-limit survival curves were constructed, and median survival times were calculated using SAS PROC LIFETEST [15]. The median survival time is the time at which half of the subjects reached ESRD or death. The log rank test was used to compare survival curves. A *P* value of < 0.05 was

Figure 1. Chemical composition of stones in ADPKD patients.

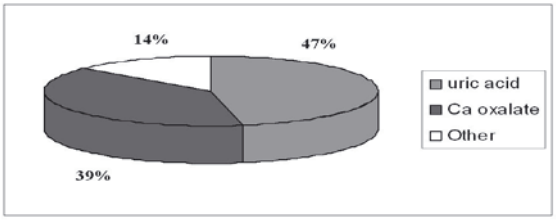
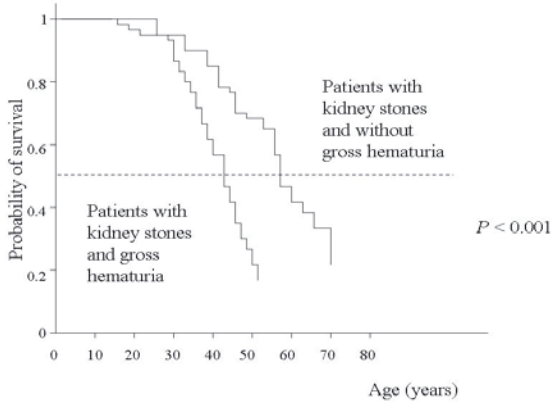


Figure 3. Comparison of renal survival between patients with kidney stones and with and without gross hematuria.



considered significant. Risk ratios (RR) were calculated using the Cox proportional hazards model [16].

3. Results

Demographic data of patients included in the study are given in Table 1. Kidney stones were present in 116 of our patients with ADPKD (58%), with an average age 46.4±5.7 years old (range from 17 to 67 years old). Sixty-five patients with kidney stones (56%) were females (Table 1). In 51 patients (44%) the detection of renal stones was done by renal ultrasound, in 19 patients (16%) was done by KUB, in 8 patients (7%) was done by intravenous pyelography and in 38 patients (33%) was done by CT scan.

75% of patients with nephrolithiasis were symptomatic for kidney stones, and only four of them (3.6%) presented with hydroureteronephrosis that required surgical stone removal.

The stones were associated with an abnormally low urinary pH (5±0.3) in 72 patients (62%). Sixty-three patients with nephrolithiasis (54%) have eliminated kidney stones which were evaluated with spectral analysis and their composition is given in Figure 1.

In patients with nephrolithiasis hypercalciuria was found in 12%, hyperuricosuria in 42%, hypocitraturia in 43%, hyperoxaluria in 17% and hypomagnesuria in

Figure 2. Comparison of renal survival between patients with and without kidney stones.

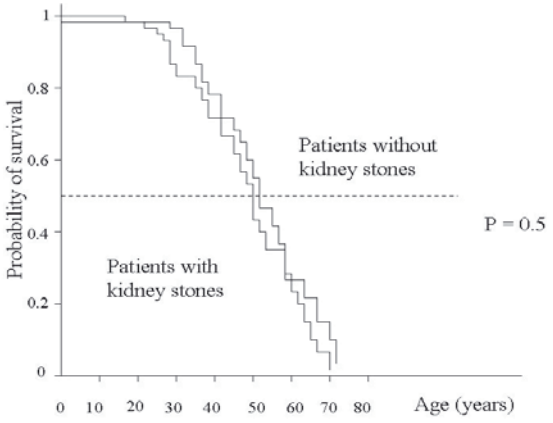
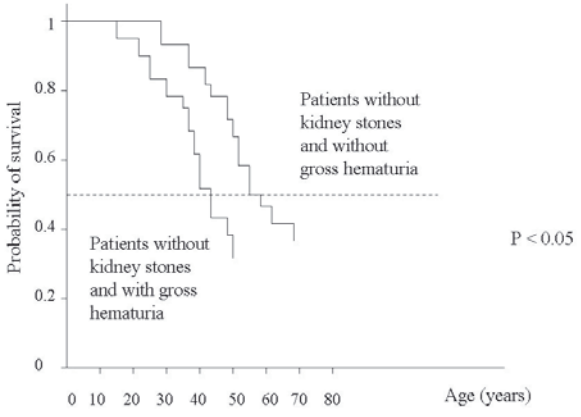


Figure 4. Comparison of renal survival between patients without kidney stones and with and without gross hematuria.



23%. There was no difference in metabolic abnormalities between the patients with calcium oxalate stone and the patients with uric acid stones. In 60% of patients with kidneys stones (70 patients) the presence of stones was associated with a history of urinary tract infections (UTI) and flank pain. UTI were more frequent in women (41 patients) than in men (29 patients). In 65 patients (56%) the kidneys stones were associated with episodes of gross hematuria.

Except hyperuricemia that was observed in 28% of patients, the seric levels of calcium, phosphate and magnesium were normal.

The patients with kidney stones were compared with regard to the renal survival with patients without kidney stones and there was no significant difference in renal survival between those patients (P=0.5) (Figure 2). On the other hand, patients with kidney stones and gross hematuria had a poorer renal survival than those with kidney stones but without gross hematuria (median survival 44 years vs. 55 years, P<0.001, RR=2.8) (Figure 3). Also, there was a significant difference in

renal survival between patients without kidney stones and with gross hematuria compared with those without kidney stones and without gross hematuria (median survival 43 years vs. 52 years, P<0.05, RR=2.6) (Figure 4).

4. Discussion

Kidneys stones are a frequent complication of ADPKD and are reported to occur in 11% to 34% of patients [2-8]. In our study it was present in 58% of patients, more than the prevalence reported in literature.

The reasons for this increased prevalence of stone disease range from metabolic abnormalities (hypocytraturia, hyperuricosuria, hyperuricemia and low urine pH) to anatomic abnormalities (large, obstructing cysts and dilated tubular lumens may create

tubular stasis, which predisposes to stone formation). The low urinary pH can contribute to the formation of stones from uric acid.

Recent reports suggest that the etiology of stone disease in ADPKD is multifactorial in nature, including both anatomic and metabolic factors [17,18]. Also, in this high frequency contribute some risk factors such socioeconomic status of patients, geographic zones and dietary habits (most of them were from rural areas, consuming less water, more vegetable and animal proteins).

A recent paper by Nishiura [19] seeks to address the risk factors for nephrolithiasis at a total of 125 patients with ADPKD. Although the researchers found a high prevalence of metabolic abnormalities in ADPKD patients (especially hypocitraturia) there were no excessively increased risk of stone formation in the presence of such metabolic abnormalities.

Because patients with ADPKD have a frequent occurrence of renal calcifications, the CT scan provides an excellent technique for detecting calcifications and for distinguishing renal calculi from cyst calcifications in patients with ADPKD [6]. In our study for detecting urinary calculi, all patients with ADPKD submitted a renal ultrasound or KUB. Intravenous pyelography is now less commonly used due to the improved sensitivity of CT scan. A large clinical study by Jackman et al concluded that KUB is more sensitive than CT scan for detecting radiopaque nephrolithiasis. Of the stones visible on KUB, 51% were not seen on CT scan [20].

KUB can be used to diagnose a renal stone in conjunction with a CT scan (when available). However, when combined with CT scan, KUB can provide a better understanding of size, shape and location of stones, and can help follow stone progress.

Since CT scan is costly and has radiation exposure, we used it only in some difficult cases. Our findings showed that CT scan was indeed better than ultrasound to detect urinary stones. 33% of our patients with undetermined stones in ultrasound or KUB, presented evident images of them on CT scan. Recently, Nishiura et al have showed that CT scan for detecting urinary stones has a sensitivity and specificity respectively 63 and 81% [19].

UTI were frequent in our ADPKD patients with kidneys stones, being more frequent in women than in men. Gross hematuria is the presenting symptom in 15–20% and occurs at least once in 30-50% of patients with ADPKD [3,21]. It may be typical presentation of intracystic haemorrhage, nephrolithiasis, and UTI or bladder cancer, especially in patients with increased risk factors for this neoplasm. Frequently, it associates the passage of kidney stones in ADPKD patients [3,21]. Gross hematuria rarely lasts for more than 7 days and blood transfusion is sometimes required. Very rarely, bleeding may be severe and persistent, notably in dialysis patients, necessitating uninephrectomy [22,23].

Interestingly in our study there is no significant difference in renal survival between patients who had and did not have kidney stones. This is due to the fact that in the group with kidneys stones there are patients without UTI and hematuria, either in the group without kidney stones there are patients with UTI and hematuria, which don't contribute in any difference between groups.

While there is significant difference in renal survival between patients with kidneys stones and gross hematuria and those with kidneys stones but without gross hematuria. On the other hand, there is a significant difference in renal survival between patients without kidney stones and with gross hematuria compared with those without kidney stones and without gross hematuria. Knowing that hematuria, except kidney stones, is caused from intracystic hemorrhage, UTI or bladder cancer, one could perhaps speculate that bleeding is a negative prognostic sign in ADPKD. These data support other previous studies from Gabow and Johnson [22,23], which point out that episode of gross hematuria may be a risk factor for renal function deterioration.

We conclude that the prevalence of nephrolithiasis in ADPKD in Albania is high. This fact need to be followed by more studies in order to explore other possible factors, which might contribute to a high prevalence of ADPKD in our country. Also the high prevalence of nephrolithiasis demands a greater care for our patients in order to prevent the well known complications on time.

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