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Araştırma

Evaluation of Nephrolithiasis Risk Factors in Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Single Center Experience

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ABSTRACT

Objective: *Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease and nephrolithiasis is frequent among ADPKD patients compared with general population. In this study, we aimed to review the factors associated with the development of kidney stones in ADPKD patients.*

Material and Methods: *A total of 118 ADPKD patients were retrospectively evaluated. Demographic characteristics, serum biochemistry, and clinical features were compared in stone formers and non-stone formers.*

Results: *Twenty-eight patients (23.7%) were diagnosed with kidney stones. History of frequent urinary tract infections (UTIs), the presence of liver cyst and gross hematuria were found to be associated with the presence of kidney stones.*

Conclusion: *According to our findings nephrolithiasis should be kept in mind in ADPKD patients with liver cyst, hematuria, and recurrent UTIs.*

Keywords: *nephrolithiasis, autosomal dominant polycystic kidney disease, liver cyst*

ÖZ

Otozomal Dominant Polikistik Böbrek Hastalarında Nefrolitiazis Risk Faktörlerinin Değerlendirmesi: Tek Merkez Deneyimi

Amaç: *Otozomal Dominant Polikistik Böbrek (ODPKB) Hastalığı, en sık görülen kalıtsal böbrek hastalığıdır ve nefrolitiyaz genel popülasyonla karşılaştırıldığında bu hastalarda daha sıktır. Çalışmamızda, ODPKB hastalarında böbrek taşı gelişimi ile ilişkili faktörleri gözden geçirmeyi amaçladık.*

Gereç ve Yöntem: *Toplam 118 ODPKB hastası geriye dönük olarak değerlendirildi. Taş oluşturanlar ve taş oluşturmayanlar arasında demografik özellikler, serum biyokimyası ve klinik özellikler karşılaştırıldı.*

Bulgular: *Yirmi sekiz hastada (%23,7) böbrek taşı tespit edildi. Tekrarlayan idrar yolu enfeksiyonu (İYE) öyküsü, karaciğer kisti varlığı ve gros hematüri böbrek taş varlığı ile ilişkili bulunmuştur.*

Sonuç: *Bulgularımıza göre karaciğer kisti, hematüri ve tekrarlayan İYE'li ODPKB hastalarında nefrolitiyaz olabileceği akılda tutulmalıdır.*

Anahtar kelimeler: *nefrolitiazis, otozomal dominant polikistik böbrek hastalığı, karaciğer kisti*

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD), which eventually progresses to end stage renal disease (ESRD), is the most common inherited kidney disease. It is the cause of ESRD with a rate of 5-10%. Even though the incidence is the same for both males and females, progression to ESRD is higher in males [(1)]. ADPKD is caused by mutations in either PKD1 gene (on chromosome 16) or PKD2 gene (on chromosome 4) which encode polycystin-1 and polycystin-2 respectively [(2)].

ADPKD has both renal and extrarenal manifestations. Extra-renal manifestations are cardiovascular problems, and extrarenal cysts like hepatic and pancreatic

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cysts. Renal manifestations include multiple bilateral renal cysts, loss of renal function, kidney stones, vulnerability to infections and loss of renal function. The deficiency in urine concentrating ability of kidney usually appears as the first manifestation and this is followed by formation of cysts [2].

Kidney stones are common in ADPKD patients compared with the normal population [3,4]. Anatomical factors such as increased renal volume and several metabolic impairments including low urine Ph and volume, hypocitraturia, hyperoxaluria, hyperuricosuria, hypomagnesemia, and possible distal acidification defects contribute to the development of renal stones [3,5-7]. Furthermore, other risk factors including body mass index (BMI), hypertension (HT), education level, hepatic cysts and age, were mentioned as risk factors for stone formation in previous studies [8]. History of UTIs is another risk factor for stone formation. Expanding cysts compress the collecting system producing urinary stasis may predispose to stone formation and infection. Early diagnosis and the management of the renal stones are important to prevent progression to the ESRD and acute decline in renal functions.

In this study, we aimed to review the prevalence of kidney stones and associated risk factors for the development of kidney stones in ADPKD patients at our center.

MATERIAL and METHODS

Patients who were referred and diagnosed with ADPKD in our tertiary reference center between 2010 and 2016 were included in the study. Following institutional board review and obtaining informed consent from all of the participants, they were questioned for age, sex, smoking, education level, HT, hematuria, history of kidney stones, urinary infections, previous urinary operations and extrarenal history of any cysts according to the Turkish Nephrology Society Cystic Kidney Disease Working Group online database. After gathering measurements of patients' heights and weights, BMI was calculated. Diagnosis of ADPKD was made based on family history and ultrasonographic diagnostic criteria described by Y. Pei et al. [9].

Resting seated blood pressure was measured two times and the average of measurements was used. Antihypertensive drug usage was noted. Biochemistry and blood lipid profile were acquired from all of the subjects after eight hours of fasting. Spot urine microalbumin/creatinine ratio was obtained from the patients without menstrual bleeding or active UTIs. Those with microalbumin/creatinine ratios smaller than 20 mg/gr were categorized as normoalbuminuria, those with ratios between 20 mg/gr and 300 mg/gr were categorized as microalbuminuria. Glomerular filtration rates (eGFR) of the patients were estimated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. Patients on dialysis treatment and whose eGFR was less than 30 ml/min were excluded from the study.

Kidney stones were diagnosed with at least one of imaging modalities including renal ultrasound (USG) or non-contrast computerized tomography (CT). The data were compared in the group of patients with kidney stone and those without kidney stone.

Statistical analysis was performed with the SPSS version 22 (SPSS Inc. Chicago, IL) software. The Shapiro-Wilk test was used to assess the normality of continuous variables. Continuous variables that were not normally distributed were compared with Mann-Whitney U test and presented as median (minimum-maximum). Normally distributed variables were compared student t test and presented as mean and standard deviation Nominal data are presented as frequencies and percentages; between-group differences were tested by chi-square test. P value ≤ 0.05 was considered statistically significant.

RESULTS

Twenty eight of 118 ADPKD patients (23.7%) were diagnosed with kidney stone. A total of 10 (%35.7) patients were symptomatic for kidney stones. Lower back pain was present in all of the symptomatic patients. All of the symptomatic patients and 11 asymptomatic patients underwent a CT scan. Shock wave lithotripsy was performed in 5, percutaneous nephrolithotomy in 3 and retrograde intrarenal surgery in 2 patients. Eighteen patients were followed up conservatively. Patients were divided into two groups according stone formation. Demographic properties of patients and smoking habit were comparable between

groups; in addition GFR and blood pressure levels were not different (Table 1).

Table 1. Demographic features of ADPKD with kidney stone (ADPKD + KS) and without kidney stone (ADPKD).

	ADPKD + KS n=28	ADPKD n=90	p
Gender, n (%)			0.724
Male	12 (42.9%)	42 (46.7%)	
Female	16 (57.1%)	48 (53.3%)	
Age (year	29 (17-70)	29 (18-57)	0.317
Mean BMI (kg/m^2)	25.6±5.5	26.0±4.2	0.677
Education level, n (%)			
Illiterate	0 (0.0%)	4 (4.4%)	0.623
Primary school	10 (35.7%)	33 (36.7%)	
High school	9 (32.1%)	31 (34.4%)	
University	9 (32.1%)	22 (24.4%)	
Smoking, n (%)			
Never-Smoker	15 (53.6%)	52 (57.8%)	0.748
Smoker	8 (28.6%)	27 (30.0%)	
Ex-Smoker	5 (17.9%)	11 (12.2%)	
Hypertension, n (%)	18 (64.3%)	54 (61.4%)	0.781
Antihypertensive Drug, n (%)	16 (57.1%)	49 (55.7%)	0.892
SBP (mmHg)	130 (90-180)	130 (85-175)	0.933
DBP (mmHg)	80 (60-100)	80 (60-100)	0.627
eGFR (mL/min/1.73 m^2)	84.75 (14.7-123.4)	99.4 (19.3-136.5)	0.169

ADPKD: Autosomal Dominant Polycystic Kidney Disease; KS: Kidney stone; BMI: Body Mass Index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 2. Biochemistry and Urine characteristics of ADPKD with kidney stone (ADPKD + KS) and without kidney stone (ADPKD).

	ADPKD + KS (n=28)	ADPKD (n=90)	p
Blood Urea Nitrogen (mg/dL)	16.5 (9-63)	15 (9-40)	0.501
Creatinine (mg/dL)	0.93 (0.6-3.51)	0.83 (0.5-2.52)	0.141
Uric acid (mg/dL)	5.28±1.60	5.32±1.53	0.921
Total Cholesterol (mg/dL)	189.2±43.8	196.7±39.6	0.429
High-Density Lipoprotein (mg/dL)	42.2±9.4	44.3±10.3	0.272
Low-Density Lipoprotein (mg/dL)	115.7±32.5	120.7±34.5	0.595
Triglyceride (mg/dL)	141 (58-650)	121 (43-735)	0.718
Albumin (g/dL)	4.2 (0-4.7)	4.3 (3.6-5.3)	0.655
Hemoglobin (g/dL)	13.2 (10.5-16.4)	13.2 (9.8-17.7)	0.827
Hematocrit (%)	38.25 (31-50.4)	38.6 (30-53.4)	0.681
Creatinine Clearance (mL/min/1.73 m^2)	96.2 (32.1-169.4)	104.19 (31-192.5)	0.668
Proteinuria (mg/dL)	0 (0-1407)	14.5 (0-1100)	0.273
Albuminuria (mg/dL)	51 (5-487)	19 (5-536)	0.049
C-reactive protein (mg/L)	0.36 (0.3-1.28)	0.35 (0.26-7.9)	0.804
Calcium (mmol/L)	9.4±0.48	9.5±0.44	0.618
Phosphate(mmol/L)	3.5 (1-6)	3.3 (2.3-4.8)	0.220
Urine specific gravity	1013.5 (1003-1024)	1015 (1004-1034)	0.154
Urine pH	5.5 (5-7.5)	5.5 (5-7.5)	0.887

ADPKD: Autosomal dominant polycystic kidney disease; KS: Kidney stone, ADPKD: Autosomal dominant polycystic kidney disease; KS: Kidney stone

Comparison of the serum and urine samples of both groups was summarized in Table 2. There were no statistically significant difference between stone formers and non-stone formers.

Some clinical and radiological features of the groups were listed in Table 3. The rate of the macroscopic hematuria was 25% in patients with kidney stone and 9% in patients without kidney stone (p=0.027). UTIs rate was significantly higher in patients with nephrolithiasis compared with patients without nephrolithiasis (40.7% vs. 20.9%, respectively, p=0.047). Presence of liver cysts were more prevalent in stone formers than non-stone formers (53.6% vs 33.3% p=0.050, respectively).

Table 3. Radiologic and clinical features of ADPKD with kidney stone (ADPKD + KS) and without kidney stone (ADPKD).

	ADPKD + KS n=28	ADPKD n=90	p
Macroscopic hematuria, n (%)	7 (25.0%)	8 (9.0%)	0.02*
UTIs, n (%)	11 (40.7%)	18 (20.9%)	0.04*
Liver Cysts, n (%)	15 (53.6%)	30 (33.3%)	0.05*

**p≤0.05*
ADPKD: Autosomal dominant polycystic kidney disease; KS: Kidney stones; UTIs:Urinary tract infections

DISCUSSION

Kidney stones are 5 to 10 times more frequent in patients with ADPKD than general population [10]. In previous studies, the prevalence of kidney stones was found to range between 13.3% [11] to 58% [12] of the patients with ADPKD. In the present study 23.7% of our patients had nephrolithiasis in accordance with the rate of other studies.

Kidney stones can cause symptoms including lower back pain, hematuria and UTIs. The ADPKD patients may have similar symptoms as well as they might be asymptomatic. Presence of lower back pain does not always necessarily suggest nephrolithiasis in ADPKD patients. Enlargement of the cysts, their rupture or infection could be the reason of lower back pain [13]. Approximately 1 out of 4 patients was reported to be symptomatic [3,14]. In the present study the rate of symptomatic patients was 35.7% and the lower back pain was the predominant symptom.

Gross hematuria is a common symptom of patients with ADPKD. This can be an indicator of cyst rup-

ture, and nephrolithiasis rarely may be sign of renal cell carcinoma furthermore gross hematuria is a risk factor for renal progression [15,16]. In our series there was a significant predominance of gross hematuria in patients with nephrolithiasis. The rate of macroscopic hematuria with and without nephrolithiasis was 25% and 9% respectively (p= 0.027).

Recurrent UTIs can be a manifestation of kidney stones [17]. In our study, UTIs rate was significantly higher in patients with nephrolithiasis compared with patients without nephrolithiasis. This relation was also mentioned in older studies in the literature [4,18]. Enlarged cysts concurrently may predispose to cyst formation and susceptibility to infections. Increased kidney volume in ADPKD patients are well-known risk factor for renal progression [19].

The diagnosis of nephrolithiasis can be challenging. CT has higher accurate rates of detecting kidney stones when compared to other diagnostic modalities [4]. Nishiura et at al. [8] demonstrated kidney stones in 32 patient with CT. However, USG was unable to detect the kidney stones in 20 patients. The kidney stones may be missed with the USG due to large volumes of the kidney and they may be misdiagnosed because of calcification of the cyst. Every symptomatic patient in our study underwent a CT scan due to these limitations of USG.

There are several metabolic and anatomic risk factors for development of renal stones. In general population age and BMI has been found to be an important factor for development of kidney stones [20]. In a recent study, Bajrami et al. [12] reported a significant effect of age, HT and BMI on nephrolithiasis in group of patients with ADPKD. However, this relation was not shown by Nishiura et al. [8] except from mean ages of the patients. Similarly, we did not find any significant relation with any of these factors.

In the present study, the presence of hepatic cysts was found to be related with nephrolithiasis. Although Nishiura et al. [8] reported a higher rate of kidney stones in patients with hepatic cyst; this relation was not reported as statistically significant. To best of our knowledge this is the first study reporting this association. We speculate that increased prevalence of hepatic cyst in women is an abnormality which is related with multiple pregnancies and prolonged use of estrogens that slow urine flow, may explain increased risk of nephrolithiasis in female ADPKD patients with hepatic cyst [2]. The renal volume, number of cysts and larger predominant cyst size were found to be risk factor in other studies [6-8]. Distortion effects of the larger cyst may result in urinary stasis leading stone formation.

Besides anatomical factors, metabolic factors like hypocitraturia, hyperoxaluria hyperuricosuria are stated as risk factors. It is also reported that higher levels of urine magnesium and phosphate were associated with nephrolithiasis [3,7]. As a limitation, in the present study serum or urine markers were not studied so we could not state any relation with metabolic factors.

CONCLUSION

Nephrolithiasis is a common manifestation of the ADPKD. Hepatic cysts are an indicator of this accordance. Patients with hematuria and recurrent urinary tract infections should be evaluated properly for a prompt and accurate management.

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