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Demographic and Clinical Characteristics of Patients with Autosomal Dominant Polycystic Kidney Disease: A Multicenter Experience

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Key Words
Autosomal dominant polycystic kidney disease · Demographics · Hypertension · Urinary tract infection · Urolithiasis

Abstract
Aim: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. It accounts for 5–10% of patients with end-stage renal disease (ESRD). The aim of this multicenter study was to investigate the demographic and clinical characteristics of patients with ADPKD. ***Methods:*** 1,139 patients with ADPKD who were followed up at 12 different centers were recruited for this study. The investigated demographic and clinical characteristics were gender, age, smoking history, educational status, the existence of hypertension, hematuria, urinary tract infection, urinary tract stones and renal replacement therapy. Patients were considered as hypertensive if they were taking antihypertensive medications or if they had blood pressure (BP) of 140/90 mm Hg or greater. If the patients were currently on antihypertensive drugs, the classes of these agents were noted. ***Results:*** 548 male and 591 female patients were included and the mean age at initial diagnosis was 37.1 ± 16.3 years. 20.3% were current smokers whereas 15% were ex-smokers. The mean systolic and diastolic BPs were 136.1 ± 29.8 and 84.9 ± 17.8 mm Hg, respectively. 63.7% used antihypertensive drugs and 73.1% of those used renin-angiotensin system blockers. 11.8% had ESRD, of which 75.8% were treated with hemodialysis. ***Conclusion:*** This study showed that hypertension is the most common (72.6%) clinical finding in ADPKD patients in Turkey and renin-angiotensin system blockers are widely used.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease [1]. It affects between 1 in 400 and 1 in 1,000 individuals [2]. Its prevalence is higher than that of Huntington's disease, hemophilia, sickle cell disease, cystic fibrosis, myotonic dystrophy and Down syndrome combined [1, 3]. It occurs

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worldwide and in all races and ethnic groups, accounting for approximately 5–10% of end-stage renal disease (ESRD) [3, 4].

The gene for PKD1, which is localized to chromosome 16, is associated with polycystin-1 protein and is responsible for 85% of the ADPKD patients. The gene for PKD2 found in chromosome 4 accounts for 15% of ADPKD and is associated with the polycystin-2 protein [1]. These gene products are plasma membrane proteins and components of a novel signaling pathway that regulates epithelial cell growth and differentiation [5, 6].

ADPKD is characterized by the development of multiple cysts in the kidneys and other organs. Patients can present at any age, but more often come to clinical attention after the age of 30 [7]. Although palpation of the abdomen occasionally suggests the presence of ADPKD, radiographic procedures are necessary for the definite diagnosis [3, 7]. ADPKD may be clinically characterized by abdominal pain, hypertension and episodes of gross hematuria, polyuria, urinary tract stones, urinary infections, headache, aortic and cerebral aneurysms, mitral valve prolapse, and polycystic liver disease [2–4, 7].

Subsequent interstitial fibrosis developing in both kidneys leads to renal failure in 50% of affected persons by the age of 60 years [8]. According to the United States Renal Data System, ADPKD accounted for 2.51% of ESRD between 1994 and 2003 [9]. Patients who are diagnosed before the age of 30 have a worse renal survival. Male sex, PKD1 gene, episodes of hematuria, and the precocity and severity of hypertension play an important role in the progression of renal disease to ESRD [2, 7].

The aim of this study was to investigate the demographic and clinical characteristics of patients with ADPKD followed in different centers of Turkey.

Subjects and Methods

Patients with ADPKD referred to 12 different nephrology outpatient clinics all around Turkey and who gave informed consent between January 2003 and December 2009 were included in the study. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association and the study centers were participants of the Turkish Society of Nephrology Polycystic Kidney Disease Working Group, which was initiated on March 30, 2002.

The diagnosis of ADPKD was confirmed by the presence of 5 or more renal cysts distributed between both kidneys. Demographic characteristics (e.g. gender, age, education status and smoking history), renal manifestations (e.g. hematuria, urinary system infection, urinary tract stones and renal replacement therapy) and cardiovascular manifestations (e.g. hypertension and mitral valve prolapse) were recorded on the web-based data recruitment forms. If the patients were currently on antihypertensive drugs; the classes of these agents were noted. Extrarenal manifestations, including the presence of hernias, liver cysts and colonic diverticuli, were also registered.

Serum creatinine, 24-hour urinary protein excretion and glomerular filtration rates (according to the Cockroft-Gault formula in adults and the Schwartz equation in children) were also noted.

The blood pressure (BP) of the patients was measured 2 times after 10 min of rest in the sitting position with the manual manometer in the outpatient clinic by a single observer. Patients with a BP >140/90 mm Hg and those on antihypertensive medications were classified as hypertensive patients. The target BP was <130/80 mm Hg.

Urinary system infection was defined as an infection confirmed by positive urinary culture only. The presence and absence of urinary tract stones had been confirmed by ultrasonographic examination and/or a history of passing stones. Furthermore, abdominal ultrasonography was used to evaluate liver cysts and M-mode echocardiography was the method of imaging for mitral valve prolapse.

Statistical analysis was carried out with the Statistical Package for Social Sciences for Windows version 13.0 (SPSS Inc., Chicago, Ill., USA). All data were analyzed. Numerical variables were given as means ± SD and percent variations.

Results

1,139 (548 male, 591 female) patients were identified during the study period, and 656 (57.6%) patients had a positive family history of ADPKD. The patients were aware of their diagnosis for 4.5 ± 3.7 (0–27) years at initial presentation to the study centers. The mean age of the patients at the time of diagnosis was 37.1 ± 16.3 (4–82) years. 17.8% of the patients were graduates of a university; 44.3% of primary school, 15.2% high school and 22.7% were graduates of secondary school. 64.4% of the patients had never smoked; 20.3% were current smokers whereas 15% were ex-smokers (n = 765, fig. 1).

The mean serum creatinine was 2.2 ± 2.2 mg/dl and glomerular filtration rate was 69.3 ± 42.5 ml/min (n = 907). The mean daily proteinuria was 597.8 ± 1,224.7 (3–12,840) mg (n = 323).

The mean systolic BP was 136.1 ± 29.8 mm Hg and the mean diastolic BP was 84.9 ± 17.8 mm Hg. The mean arterial pressure was 104 ± 16.6 mm Hg. The mean arterial pressure was negatively correlated with glomerular filtration rate ($r = -0.26$, $p = 0.001$).

828 (72.6%) patients had hypertension and 311 (27.3%) patients were normotensive. Among the hypertensive patients, 727 (87.8%) were taking antihypertensive drugs. Blood pressure was under control in 49.5% of the subjects (fig. 2).

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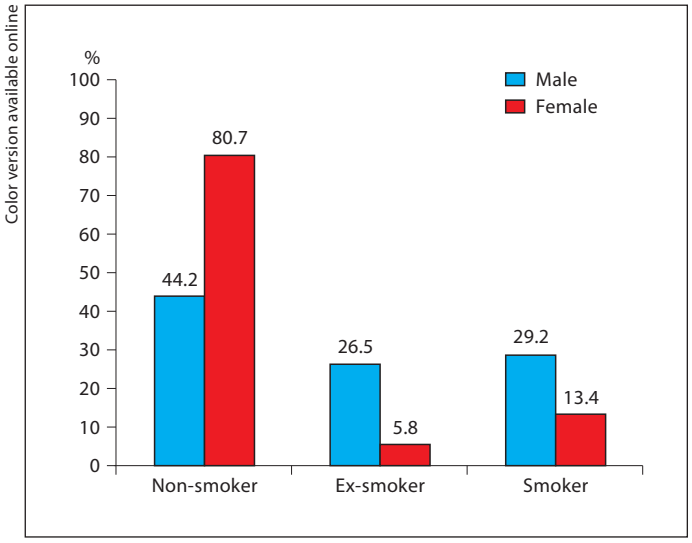

Fig. 1. History of smoking.

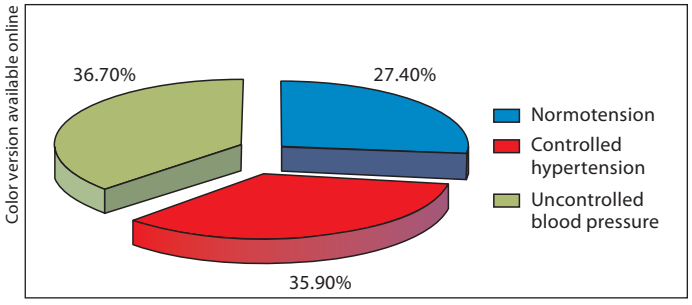

Fig. 2. The presence of controlled and uncontrolled hypertension.

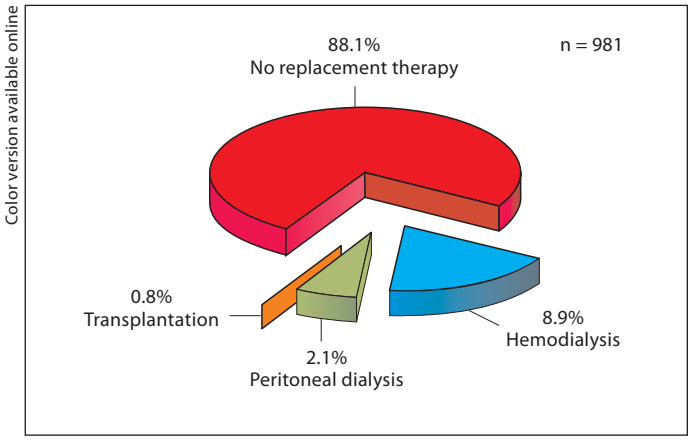

Fig. 3. Renal replacement therapies. 865 patients did not require any renal replacement therapies. 88 patients received hemodialysis; 20 patients were on peritoneal dialysis and 8 patients had been transplanted.

The use of antihypertensive drugs was as follows: 21.8% diuretics (159 patients), 20.4% β-blockers (149 patients), 39.4% calcium channel blockers (287 patients), 73.1% renin-angiotensin system blockers including angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARB; 532 patients), and 9.6% α-blockers (70 patients).

Mitral valve prolapse was investigated in 226 patients and 18 (8%) of them had a prolapse. 225 (21.6%) patients had a history of macroscopic hematuria, 228 (22.5%) patients had documented urinary tract infections (n = 1,011) and 278 (27%) patients had urinary tract stones (n = 1,029).

500 (85.4%) patients did not have hernias, 12 (2%) had inguinal and 72 (12%) patients had umbilical hernias. Liver cysts were investigated in 885 patients and cysts were demonstrated in 335 (37.9%) of those patients. Colonic diverticuli was investigated in 44 patients and 4 of them had diverticuli.

88.1% of the study population did not need any renal replacement therapy (fig. 3). Hemodialysis was the primary renal replacement therapy in 75.8% of patients requiring renal replacement therapy. The mean age of patients requiring renal replacement therapy was 46.9 ± 11.9 years.

Discussion

Polycystic kidney disease is characterized by countless epithelium-lined cysts containing urine-like fluid that is diffusely scattered throughout the renal cortex and medulla [2, 3]. The disease occurs worldwide in all races and ethnic groups. Approximately one half of affected subjects will experience minimal morbidity, whereas the remainder will have complications to a variable degree [3]. ADPKD is a dominantly inherited systemic disorder equally inherited in men and women, but ADPKD women have a slower rate of progression to renal failure with a later age of entry into ESRD as compared with men [10, 11]. Most affected patients do not experience symptoms and escape detection until middle age. It is estimated that less than one half of these cases will be diagnosed during the patient's lifetime, as the disease is often clinically silent [3, 11]. During the silent years, the renal cysts progressively expand. The kidney enlargement may not be noticed until the seventh or eighth decade of life [3]. The mean age of our patients at the time of diagnosis was 37.1 ± 16.3 years and they were aware of their diagnosis for 4.5 ± 3.7 years at initial presentation to the study centers.

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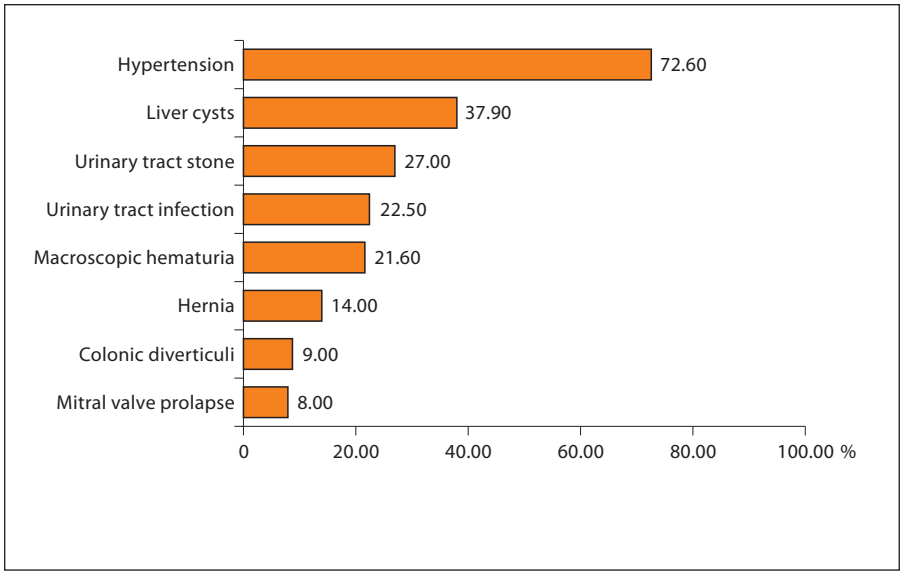

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Fig. 4. Prevalence of clinical findings.

Patient education is essential during follow-up for chronic diseases. It has been reported that with an extensive education program for both ADPKD patients and their primary care physicians, the rate of blood pressure control can be increased significantly [12]. As early treatment of hypertension in patients with ADPKD is a potential means by which beneficial renal and cardiovascular effects may be achieved, patient education programs should be carefully planned to inform any patient.

Even though we do not have enough scientific data about smoking and its specific effect on ADPKD, we predict that by increasing cardiovascular morbidity and mortality rates, smoking may accelerate the transition phase to an ESRD besides being a risk factor in ESRD [13]. A retrospective multicenter European case-control study showed that smoking is an independent risk factor for ESRD in patients with inflammatory and noninflammatory renal disease, i.e. polycystic kidney disease. The pathogenesis of the smoking-related renal damage is largely unknown. The intermittent increase in BP during smoking seems to play a major role in causing renal damage [13, 14]. Among our study population, 20.3% were smoking and 15% had quit smoking. According to a previous single center analysis, 122 ADPKD patients were examined and it was found that 11.8% of the patients were smoking and 29.4% had quit smoking [15]. All of our patients were informed about the potential effects of smoking and advised to quit.

Hypertension accelerates the transition of ADPKD to ESRD [1, 2, 7, 16]. The current multicenter study showed that hypertension is the most common clinical finding among our patients (fig. 4). This result correlates with the results of Schrier's study demonstrating hypertension in 578 (71%) of their patients [8]. Hypertension is associated with a substantial incidence of left ventricular hypertrophy (LVH) [5]. Increased left ventricular mass and hypertrophy have been found in early stages of ADPKD [17]. Cardiovascular events are the most common cause of death in ADPKD patients [18]; therefore, the major cardiovascular risk factors, hypertension and LVH, should be controlled as early as possible [1, 2, 5, 17]. A 7-year prospective, randomized study in 75 hypertensive patients with ADPKD and LVH compared the effects of rigorous and standard blood pressure control (<120/80 vs. 135–140/85–90 mm Hg) on LVH and renal function [19]. Both strategies decreased LVH significantly; however, rigorous blood pressure control was significantly more effective in decreasing left ventricular mass index than standard blood pressure control. Only 49.5% of our patients were at their target BP. Similarly, Memili et al. [15] determined the prevalence of hypertension among ADPKD patients as 72.1% in their analysis, and in only 42.9% of the hypertensive patients, BP was controlled.

There are several experimental and clinical observations that show an increased activity of the renin-angiotensin-aldosterone system in ADPKD patients. Given the potential detrimental renal and cardiac effects of angiotensin II, it is reasonable to treat hypertensive ADPKD patients with ACE inhibitors or ARB [20]. Inhibitors of the renin-angiotensin-aldosterone system decrease and

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prevent LVH and cardiac complications as they slow the progression to ESRD [1, 8, 19, 20]. In our study, 532 patients (73.1%) were on ACE inhibitors or ARB.

Patients frequently present with hematuria as the initial manifestation of ADPKD. Hypertensive ADPKD subjects are more likely to have gross hematuria than normotensive subjects and those with gross hematuria have larger renal size [21]. Nephrectomy might be considered if life threatening hematuria develops. 21.6% of our patients had macroscopic hematuria and most were hypertensive, but none of them needed nephrectomy.

Symptomatic lower urinary tract infection affects 50–75% of all polycystic patients at any given time [22]. Our study demonstrated that 22.5% patients had a confirmed urinary tract infection. Though no statistically significant differences in the frequency of any manifestations of ADPKD between men and women were found, the frequency of symptoms consistent with urinary tract infections tended to be higher in women than in men [23]. Most of the patients with urinary infection were female in our study, similar to previous reports [3].

The prevalence of urinary tract stones is considerably greater in patients with ADPKD than in the general population [24]. The composition of the stones is most frequently uric acid and/or calcium oxalate. Metabolic factors are important in their pathogenesis. Distal acidification defects may be important in a few patients, while an abnormal ammonium transport, low urine pH and hypocitraturia are the most common abnormalities [25]. Urinary tract stones precipitate the onset of renal failure, but the treatment of these stones in ADPKD patients is not different from that in patients without ADPKD [24, 25]. Ultrasonographic examination of the urinary system is a necessary and useful procedure to determine urinary tract stones. We determined these stones in 27% of the patients by ultrasonographic examination. Memili et al. [15] found a higher incidence of renal calculi (32.8%) in their patients.

ESRD develops sooner in the patients with progressive factors [1, 2, 7, 17]. The PKD1 gene, younger age at diagnosis, male gender, hypertension, increased left ventricular mass, hepatic cysts in women, 3 or more pregnancies, gross hematuria, urinary tract infections in men and increased renal volume are factors associated with worse renal function in ADPKD [26]. While 88 patients required hemodialysis, 20 of them were treated with peritoneal dialysis. Only 8 had undergone renal transplantation.

In conclusion, since penetrance of polycystic kidney disease is 100%, it should definitely be investigated in suspected cases and among their family members at the same time. The presence of potential risk factors such as gender, age, smoking, clinical renal manifestations and hypertension should be questioned and investigated at the first appointment in order to slow the progression of the disease.

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