

Extrarenal Manifestations of Autosomal Dominant Polycystic Kidney Disease

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Recently, with the widespread use of new imaging techniques, the diagnosis of autosomal dominant polycystic kidney disease (ADPKD) is increasing. To analyze the extrarenal manifestations of ADPKD in Korean patients, we retrospectively studied the clinical characteristics of 30 patients with ADPKD. Thirty Patients with ADPKD who had been diagnosed at Yongdong Severance Hospital from 1988 through 1994 were recruited for this study. All patients' past and family histories were re-evaluated, and charts and radiologic images were reviewed retrospectively. The male to female ratio was 9:21, and the age of initial diagnosis was 39.2 ± 13.8 (mean \pm SD) years. In 15 cases (50%), ADPKD had been diagnosed by renal symptoms; in 8 cases (26.7%), by chance during evaluation of extrarenal diseases; in 5 cases (16.7%), by family screening; and in 2 cases (6.7%), by uremic symptoms. Extrarenal involvement included hepatic cysts (70%), pancreatic cysts (16.7%), splenic cysts (6.7%), thyroid cysts (6.7%), inguinal hernia (3.3%), and colonic diverticula (3.3%). In 5 cases (16.7%), cardiac valvular abnormalities were noted by echocardiography. Seven patients underwent hemodialysis, and the duration from the initial diagnosis to initiation of dialysis was 9.9 ± 8.5 (mean \pm SD) years. We investigated the extrarenal manifestations of 30 cases of ADPKD in Koreans, which were also common and clinically important as renal manifestations. Renal cysts are only one of a myriad of renal and extrarenal manifestations of ADPKD. ADPKD should be managed systematically since this disorder is a systemic disease with clinically important involvement of the cardiovascular system, the gastrointestinal tract, the genitourinary system, and the musculoskeletal system.

Key Words: ADPKD, extrarenal manifestation

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic diseases and by far the most common inherited kidney disease. Recently, new interest has arisen producing

insights into the genetics, the cellular alterations producing cyst growth and development, and the clinical manifestations of ADPKD (Gabow, 1990). As in any autosomal dominant disease, a patient with ADPKD must have the defective gene on one of a pair of autosomal chromosomes. Therefore, each offspring of an affected individual has a 50% chance of inheriting the chromosome carrying the defective gene, and thus inheriting the disease (Gabow and Grantham, 1997). The clinical phenotype can result from at least 2 different gene defects. One gene (PKD1) that can cause ADPKD is located on the short arm of chromosome 16 (Reeders *et al.*

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1985). The location of the other ADPKD gene (PKD2) is chromosome 4 (Kimberling *et al.* 1993). The third gene (PKD3) has not yet been assigned to a chromosomal segment. The number of families with disease linked to neither chromosome 16 nor chromosome 4 is steadily increasing and it is likely that a connection will soon be established (Daoust *et al.* 1995). This discovery has made it possible to develop new methods for diagnosing the disorder in gene carriers prior to the development of renal cysts. Although renal cysts are clearly an important manifestation of the gene defect, other renal and extrarenal manifestations are both common and clinically important. Cardiac valvular lesions, intracranial aneurysms, hepatic cysts, and uterine or ovarian cysts are included in the array of systemic manifestations (Gabow, 1990).

In Western countries, ADPKD currently accounts for 3.1-to-10% of all end-stage renal disease (Gardner and Evan, 1984; Gabow, 1990; Zeier *et al.* 1996). Its prevalence ranges from 1 in 200 to 1 in 1,000, and it seems to be less common in black than in white subjects (Dalgaard, 1957; Iglesias *et al.* 1983; Gardner and Evan, 1984). In Korea, it accounts for 1-to-2% of end-stage renal disease (Yang *et al.* 1985; Kim *et al.* 1989). Recently, with widespread use of new imaging techniques, diagnosis of ADPKD seems to be increasing in Korea and more interest should be given to this common and clinically important disease. To elucidate extrarenal manifestations of ADPKD in Korean patients, we analyzed the clinical characteristics of 30 patients recruited from our renal clinic.

MATERIALS AND METHODS

Thirty patients with ADPKD who had been diagnosed at Yongdong Severance Hospital from 1988 to 1994 were recruited for this study. The diagnosis of ADPKD was confirmed when the presence of bilateral renal cysts, totalling 5 or more, were visualized by ultrasonography or computed tomography, with positive family history or extrarenal manifestations such as hepatic cysts, aneurysms of cerebral arteries, and cysts of the pancreas (Welling and Grantham, 1991). All patients' past and family his-

stories were re-evaluated and charts and radiologic films were reviewed retrospectively.

Patients' age at the initial diagnosis, sex, past and family histories, symptoms and signs, laboratory data, electrocardiogram, abdominal or other organ ultrasonography, computed tomography (CT), echocardiography, and other study data including barium enema and brain CT scan were analyzed.

RESULTS

The male to female ratio was 9 : 21. Family history of ADPKD was positive in 17 cases (56.7%). Mean age of the initial diagnosis was 39.2 ± 13.8 (mean \pm SD) years, and in 21 cases (70%), the first diagnosis of ADPKD had been made in the patients' 30's and 40's (Table 1). In 15 cases (50%), ADPKD had been diagnosed by renal symptoms, such as abdominal or flank pain, mass, gross hematuria, and symptoms of renal infection; in 8 cases (26.7%), by accident during the evaluation of extrarenal diseases or health screening; in 5 cases (16.7%), by family screening due to positive family history; and in 2 cases (6.7%), by uremic symptoms (Table 2).

All the subjects had undergone abdominal ultrasonography more than once, 11 patients had undergone abdominal computed tomography and in 5 cases, intravenous pyelography had also been done. Extrarenal manifestations and their frequencies are

Table 1. Age distribution of ADPKD¹ at the initial diagnosis

| Age | Number of patients (%) |
|-----------|------------------------|
| ≤ 10 | 1 (3.3) |
| 11~20 | 2 (6.7) |
| 21~30 | 3 (10.0) |
| 31~40 | 9 (30.0) |
| 41~50 | 12 (40.0) |
| 51~60 | 1 (3.3) |
| 61~70 | 2 (6.7) |
| ≥ 71 | 0 (0.0) |
| Total | 30 (100) |

¹ : autosomal dominant polycystic kidney disease

Table 2. Routes of the initial diagnosis

| Route | Number of patients (%) |
|--------------------|------------------------|
| Renal symptoms | 15 (50.0) |
| Accidentally found | 8 (26.6) |
| Positive FHx* | 5 (16.7) |
| Uremic symptoms | 2 (6.7) |
| Total | 30 (100) |

* : family history of ADPKD

Table 3. Extrarenal manifestations of ADPKD

| Manifestations | Number of patients (%) |
|------------------------------|------------------------|
| Gastrointestinal | |
| Hepatic cysts | 21/30 (70.0) |
| Pancreatic cysts | 5/30 (16.7) |
| Splenic cysts | 2/30 (6.7) |
| Diverticulosis | 1/30 (3.3) |
| Hernia | 1/30 (3.3) |
| Genitourinary | |
| Ovarian cysts | 3/21 (14.3) |
| Uterine cysts | 3/21 (14.3) |
| Testicular cysts | 1/ 9 (11.1) |
| Cardiovascular | |
| Valvular abnormalities | 5/30 (16.7) |
| Subarachnoid hemorrhage | 1/30 (3.3) |
| Miscellaneous | |
| Thyroid cysts | 2/30 (6.7) |
| No extrarenal manifestations | 4/30 (13.3) |

shown in Table 3. Gastrointestinal manifestations included hepatic cysts in 21 cases (70.0%); pancreatic cysts in 5 cases (16.7%); splenic cysts in 2 cases (6.7%); inguinal hernia in 1 case (3.3%); and colonic diverticula in 1 case (3.3%). In 21 patients with hepatic cysts, 2 patients (9.5%) had a history of hepatic cyst infection, and 1 patient (4.8%) had history of hepatic cyst rupture with hemoperitoneum. Two hepatic cyst infections were caused by *E. coli* and *Enterococcus fecalis* respectively, combined with septicemia and required surgical interventions. Five out of 30 patients had undergone barium enema due to large bowel symptoms and one case of colonic diverticula was found. Fourteen out of 21 female patients had undergone pelvic ultrasonography or computed tomography. Ovarian and uterine cysts were found in 3 cases (14.3%) for

Table 4. Hypertension in ADPKD

| | Serum creatinine | | Total |
|-------------------------------------|------------------|--------------|--------------|
| | < 1.2 mg/dl | ≥1.2 mg/dl | |
| Number of hypertensive patients (%) | 9/16 (56.3) | 13/14 (92.9) | 22/30 (73.3) |

each, respectively. In 1 male patient, we performed a testis ultrasound examination due to testicular pain and found testicular cysts. Three out of 30 patients had undergone thyroid ultrasound examinations due to enlarged thyroid glands. Thyroid cysts were found in 2 patients (6.7%). Twelve out of 30 patients had undergone echocardiography due to cardiac murmurs. In 5 patients, cardiac valvular abnormalities were noted, including regurgitant lesions of the mitral valves with mitral valve prolapse (2 cases), tricuspid regurgitation (2 cases), and aortic regurgitation (1 case). Two patients with mitral valve prolapse also showed WPW syndrome on electrocardiography and complained of atypical chest pain. Eighteen patients (60%) had complaints of chronic headache. Four out of the 18 had undergone brain CT and one (3.3%) of those patients developed subarachnoid hemorrhage. Hypertension was found in 22 patients (73.3%). Among 16 cases whose serum creatinine concentration was less than 1.2 mg/dl, 9 patients (56.3%) were hypertensive. Thirteen of 14 cases whose serum creatinine concentration was above 1.2mg/dl, were hypertensive (92.9%)(Table 4). Extrarenal manifestations had not been found in 4 patients (13.3%). Seven patients (23.3%) underwent hemodialysis and the duration from initial diagnosis to initiation of dialysis was 9.9 ± 8.5 (mean \pm SD) years.

DISCUSSION

ADPKD is one of the most common genetic diseases and by far the most commonly inherited kidney disease. It accounts for 3.1-to-10% of all patients admitted for maintenance dialysis in Wes-

tern countries and 1-to-2% in Korea (Gardner and Evan, 1984; Yang *et al.* 1985; Kim *et al.* 1989; Gabow, 1990; Zeier *et al.* 1996). Recently, with widespread use of new imaging techniques, diagnosis of ADPKD seems to be increasing in Korea. In our study, peak age distribution of the initial diagnosis of ADPKD was at ages 41 to 50 years and this result was similar to the previous studies (Yang *et al.* 1985; Kim *et al.* 1989).

As in any autosomal dominant disease, a patient with ADPKD has the defective gene on one of a pair of autosomal chromosomes. Therefore, each offspring of an affected individual has a 50% chance of inheriting the chromosome carrying the defective gene and thus, inheriting the disease. ADPKD, which appeared clinically to be 1 entity of disease, actually results from at least 2 different gene defects. The most common gene, PKD1, is located on the short arm of chromosome 16. This discovery has made it possible for new methods to diagnose the disorder in gene carriers prior to the development of renal cysts. The location of the other gene, which has been called PKD2 or non-PKD1, is chromosome 4. The location of a third gene (PKD3) has not yet been determined. It appears that PKD1 accounts for approximately 90 percent of all ADPKD in the white population (Kimberling *et al.* 1990). The pathogenesis of ADPKD has not been established clearly. Altered epithelial cell growth, secretion, and extracellular matrix production have all been shown to contribute to the development of ADPKD (Gabow, 1991; Wilson and Sherwood, 1991). These abnormalities could, in fact, contribute to cyst development and extrarenal manifestations.

ADPKD may be revealed by renal symptoms. However, in a substantial number of cases, the disease is asymptomatic and is discovered during routine clinical examination, on abdominal ultrasonography performed for extrarenal reasons, or during genetic investigation. In our study, 50% of ADPKD cases were revealed by renal symptoms, but about 43% of patients with ADPKD had been diagnosed during the evaluation of extrarenal diseases, health screening and family screening due to a positive family history. Renal symptoms usually begin in the third or fourth decades. Common renal symptoms include flank or abdominal pain, palpable mass, hematuria, symptoms of renal infection and stones,

and nocturia. Family history may be positive for ADPKD in only about 60 percent of affected individuals (Dalgaard, 1957; Iglesias *et al.* 1983). In this study, we did not get an exact proportion of ADPKD patients with family association but 16.7% of our patients were diagnosed by family screening due to a positive family history. Although renal cysts are clearly an important manifestation of the gene defect, other renal and extrarenal manifestations are both common and clinically important. The most common extrarenal manifestation is hepatic cysts, which occur in 38-to-63% of patients (Dalgaard, 1957; Milutinovic *et al.* 1980; Gabow *et al.* 1984). Hepatic function is usually normal, and the liver cysts usually are asymptomatic, but sometimes cause epigastric discomfort or biliary colic, or become infected (Everson, 1993). Cysts also may occur in the spleen, pancreas, lungs, ovaries, uterus, testis, epididymis, thyroid, and bladder. In this study, hepatic cysts were found in 21 of 30 patients (70%), and other cysts had also been noted in the pancreas, spleen, ovaries, uterus, testis and thyroid. The prevalence of hernia in men with polycystic kidney disease was almost 5 times higher than anticipated in a general male population. It might suggest that abnormal collagen synthesis in ADPKD has a possible role in the development of a hernia (Gabow *et al.* 1984). Scheff *et al.* (1980) have reported that 83% of patients with ADPKD having chronic hemodialysis also had diverticulosis of the colon. Only 1 of our 30 patients (3.3%) had colonic diverticulosis. This low prevalence of colonic diverticulosis in our patients probably derives from the fact that our patients were not systematically evaluated with barium studies (only 5 cases had undergone barium enema in our study).

Hypertension is the most common cardiovascular manifestation, which occurs in about 70% of patients before the onset of renal insufficiency (Dalgaard, 1957). Hypertension appears to be related to the renin-angiotensin system (Bell *et al.* 1988; Chapman *et al.* 1990). The renin-angiotensin system is stimulated significantly more in hypertensive patients with ADPKD than in comparable patients with essential hypertension. The increased renin release, perhaps due to renal ischemia caused by renal cyst expansion, contributes to the early development of hypertension in ADPKD (Chapman *et al.* 1990).

Cardiac valvular lesions are common, and 26% of patients had mitral valve prolapse, often accompanied by palpitation and chest pain (Hossack *et al.* 1988; Gabow, 1990). In this study, hypertension occurred in 73% of patients and cardiac valvular lesions were noted by echocardiography in 5 cases (16.7%) which included 2 cases of MVP. Intracranial aneurysm occurred in 10-to-36% of patients with ADPKD, and rarely a subarachnoid hemorrhage is the presenting manifestation (Schievink *et al.* 1992). In our study, 1 case presented with subarachnoid hemorrhage. The natural history of renal functional impairment with ADPKD is variable. End stage renal disease may occur as early as the first decade of life, or renal function may be well maintained into the eighth decade. Approximately 50% of patients had well-preserved renal function at 70 years of age (Churchill *et al.* 1984). Renal function was less well maintained in ADPKD patients with hypertension. Other factors that influenced long-term prognosis were less well defined (Gabow *et al.* 1990). Hemodialysis is the usual mode of renal replacement therapy in patients with ADPKD, but in patients with only a moderately enlarged kidney and liver, peritoneal dialysis can also be utilized (Gabow and Grantham, 1997). Renal transplantation is as useful for ADPKD subjects as for other patients with ESRD (Lazarus *et al.* 1971; Gabow and Grantham, 1997). In our study, seven patients (23.3%) had been undergoing hemodialysis and the mean duration from the initial diagnosis to initiation of dialysis was 9.9 years.

In conclusion, ADPKD is a hereditary disease showing variable clinical characteristics and complications. We investigated the extrarenal manifestations of 30 cases of ADPKD in Koreans, which is also common and as clinically important as renal manifestations. Renal cysts are only one of a myriad of renal and extrarenal manifestations of ADPKD. ADPKD should be managed systematically because the disorder is a systemic disease with clinically important involvement of the cardiovascular system, the gastrointestinal tract, the genitourinary system and the musculoskeletal system.

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