

Autosomal dominant polycystic kidney disease in hemodialysis patients in southern Brazil

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ABSTRACT

Introduction: Autosomal dominant polycystic kidney disease is the most common hereditary renal disease in humans. **Objective:** To examine the prevalence, clinical and laboratory characteristics of patients with polycystic kidneys and relate disease manifestations by gender. **Methods:** This was an observational and retrospective study. All the medical records of patients with polycystic kidneys who initiated hemodialysis between 1995 and 2012, in four centers that treat patients of the coverage area of the 15th regional health Paraná (Brazil), were analyzed. **Results:** The study included 48 patients with polycystic kidneys, the primary cause of stage 5 CKD. Disease prevalence was one in 10,912 people. The average age of dialysis initiation was 50.7 years and the follow-up time on dialysis until transplantation (36.5 months) was lower among men. Hypertension was the most frequent diagnosis in 73% of patients, predominantly in women (51.4%). The liver cyst was the most frequent extrarenal manifestations in men (60.0%). The death occurred in 10.4% of patients using hemodialysis, and 60% of men. The class of antihypertensive drug used was that acts on the renin-angiotensin system with higher frequency of use among women (53.3%). The post-dialysis urea was significantly higher in men. **Conclusion:** The prevalence of the disease is low among hemodialysis patients in southern Brazil. The differences observed between genders, with the exception of the post-dialysis urea, were not significant. The findings are different from those reported in North America and Europe.

Keywords: autosomal dominant, chronic, dialysis, epidemiology, kidney failure, polycystic kidney, renal replacement therapy.

INTRODUCTION

The autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease in humans.¹ Recognized as a monogenic and multiple system disease, it is characterized by the development and progressive growth of multiple bilateral renal cysts that destroy the functional parenchyma, as well as extrarenal manifestations (cysts in other organs, cardiac valvular abnormalities, cerebral aneurysms, abdominal hernias, body aches, cholecystolithiasis and diverticular disease).²⁻⁵

ADPKD is genetically heterogeneous, that is, diseases which have similar phenotypic features; however, it can be caused by mutations in more than one specific gene.¹ The genes responsible are: PKD1 - located in chromosome 16p 13.3, accounted for 85% of cases;⁶ PKD2 - located in chromosome 4q 21-23, at a frequency of 10-15% of the cases;^{7,8} and possibly a third gene, PKD3, which has not yet been identified.⁹ Patients with mutations in the PKD2 gene start dialysis later (mean age of 74 years) compared to the PKD1 gene (mean age of 54 years).^{1,4,10}

The worldwide prevalence of the disease is estimated to be between 1:400 and 1:1000 persons.^{2,3,11-14} ADPKD is the third leading cause of Stage 5 Chronic Kidney Disease (CKD) and affects 5-13.4% of patients undergoing hemodialysis in Europe and in the United States^{12,15-18}, and about 3% in

Eastern countries.^{19,20} Stage 5 CKD caused by ADPKD has an annual incidence rate of 8.7 and 6.9 cases per million people (1998-2001 in the United States) and 7.8 and 6.0 per million of the population (1998-1999 in Europe), for men and women, respectively.^{2,21} Literature shows that men with ADPKD are diagnosed later than women, indicating that the male gender is a determinant in disease worsening.⁵

In Brazil, there is very little epidemiological data available on ADPKD. To our knowledge, there are no reports of epidemiological studies of patients with ADPKD on dialysis in the northwest of Paraná. Thus, this study aims to: a) assess the prevalence, clinical and laboratory characteristics of patients with ADPKD, and b) compare disease manifestations by gender.

METHODS

This is an observational and retrospective study. We reviewed the charts of all patients with confirmed diagnosis of ADPKD admitted from January 1995 to September 2012 to use renal replacement therapy (dialysis) in four dialysis centers in Maringá, Paraná state. These centers cater to the demand of patients within the area of coverage of the 15th Regional Health District of Paraná, comprising 30 municipalities in the northwest of the state, totaling 523,319 inhabitants according to the 2010 census of the Brazilian Institute of Geography and Statistics.²²

The diagnosis was based on the criteria of initial and evolutionary clinical history, family history and imaging findings, as described by Pei *et al.*:²³ three or more (unilateral or bilateral) renal cysts are sufficient to diagnose individuals aged 15-39 years, two or more cysts in each kidney is sufficient for individuals aged 40 to 59 years, and four or more cysts in each kidney is required for individuals $>$ or $=$ 60 years of age. On the other hand, less than two renal cysts in individuals at risk aged $>$ or $=$ 40 are sufficient to rule out the disease.

As a criterion for CKD stage 5 we considered the need for dialysis. Hypertension was defined based on the mean value of all systolic blood

pressure measurements \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg at rest, or patients previously diagnosed with hypertension using antihypertensive medication.²⁴

The parameters analyzed were based on sociodemographic data from renal and extrarenal manifestations in renal transplantation, family history and morbimortality of patients diagnosed with ADPKD. The clinical information obtained from the medical history before dialysis was analyzed as additional data in patients with macrohematuria, pain, urinary tract infections, hypertension and antihypertensive drugs. Various biochemical parameters measured during hemodialysis were also analyzed, such as pre-dialysis serum urea, post-dialysis urea, potassium, phosphorus, calcium, creatinine and albumin. We considered the most recent data for these variables.

To collect the data we analyzed each chart, with completion of admission forms and monitoring of each patient, and the data was stored in Microsoft Excel.

The categorical variables were expressed as percentages and the continuous variables as mean and standard deviation ($\bar{x} \pm SD$). The statistical method used was *Student's t*-test for contrasting hypotheses about mean values in populations with normal distribution. When they did not fulfill the principle of normality, we used the nonparametric Mann-Whitney test. Differences between categories were evaluated by the χ^2 test with Yates correction when necessary. Statistical analyzes were performed using the Epi Info 3.5.1 software, with significance set at $p < 0.05$.

The study was approved by the Standing Committee on Ethics in Research Involving Humans (COPEP) of the State University of Maringá (Nº. 204.772/2013).

RESULTS

We evaluated 463 hemodialysis patients from four different dialysis centers. Among these, 48 subjects, corresponding to 10.3% of the total, had a definite diagnosis of ADPKD as the primary cause of stage 5 CKD. ADPKD prevalence among s patients during

the study period was 9.2 per 100,000 inhabitants (or 1:10.912).

We found no statistical differences regarding the mean age of the patients and the age of entry into dialysis, time on dialysis and age at transplant. The demographic characteristics are summarized on Table 1.

TABLE 1 DEMOGRAPHICS OF THE PATIENTS ON DIALYSIS BY GENDER (N = 48)

Variables	Men (N = 24)	Women (N = 24)	p
Mean age (years)	53.5	56.2	0.54
Age of dialysis treatment onset (years)	50.71	51.55	0.82
Dialysis duration (months)*	36.25	39.88	1.00
Mean age at the time of transplant	53.25	55.63	0.22

* Follow-up on dialysis all the way to the transplant.

Information on ethnicity was given by the patients themselves. Caucasian patients were more frequent (72.9%), mostly of European descent. The remainder of the sample was composed of African descent (20.8%) and Asians (6.3%). These are the first epidemiological data on ADPKD for Asian descendants in Brazil.

The main clinical characteristics of the patients are shown on Table 2. Regarding kidney manifestations, the frequency of hypertension, pain and/or abdominal cramps and urinary tract infection was higher in women than in men. Macrohematuria was detected in 22 patients (45.8%), with a higher frequency in male patients. The difference between the values of the clinical features was not statistically significant between the genders.

As for extrarenal manifestations, liver cysts were detected in five patients (10.4%), more frequently in men. No other cyst was observed in any other abdominal organ by means of ultrasonography. Two cerebral aneurysms were confirmed by cerebral angiography, with equal distribution between genders (50%). The difference between the values of the extrarenal characteristics was not statistically significant between the genders.

TABLE 2 CLINICAL CHARACTERISTICS OF ADPKD PATIENTS ON DIALYSIS, BY GENDER (N = 8)

Variables	Men (N = 24)	Women (N = 24)	p
Kidney manifestations			
Arterial hypertension	17 (48.6%)	18 (51.4%)	0.34
Palpable abdominal mass	13 (59.1%)	9 (40.9%)	0.24
Macrohematuria	4 (57.1%)	3 (42.9%)	0.68
Abdominal colics and/or pain	9 (45.0%)	11 (55.0%)	0.55
Urinary infection	2 (33.3%)	4 (66.7%)	0.38
Extrarenal manifestations			
Liver cyst	3 (60.0%)	2 (40.0%)	1.00
Cerebral aneurisma	1 (50.0%)	1 (50.0%)	0.75
Other manifestations			
Diabetes Mellitus	2 (50.0%)	2 (50.0%)	0.69
Glomerulonephritis	2 (100.0%)	-	0.48
Associated events			
Nephrectomy	7 (63.6%)	4 (36.4%)	0.49
Transplant	4 (33.3%)	8 (66.7%)	0.31
Death	3 (60.0%)	2 (40.0%)	1.00
Classes of anti hypertension drugs*			
Renin-angiotensin system drugs**	7 (46.7%)	8 (53.3%)	0.81
β -blockers	11 (55.0%)	9 (45.0%)	0.53
Calcium channel blockers	4 (50.0%)	4 (50.0%)	0.53
Diuretic agents	9 (60.0%)	6 (40.0%)	0.40
Other drugs***	4 (80.0%)	1 (20.0%)	0.28

* The patients may use more than one class of agents; ** Including ACE inhibitors and Angiotensin II receptor antagonists; *** Including vasodilators and α -agonists.

Other manifestations were observed in ADPKD patients. The most common was *diabetes mellitus* in four patients (8.3%), with equal distribution between genders. Glomerulonephritis was found in only two male patients (4.2%). The difference between the values of these other manifestations was not statistically significant between the genders.

Regarding the ADPKD-related events, nephrectomy and death were more frequent among males. Kidney transplantation was performed in 12 patients (25.0%), with a predominance of women

(66.7%). The difference between the values of the disease-related events was not statistically significant between genders.

We identified five classes of antihypertensive agents. Of these, only the renin-angiotensin system (RAS) drugs were more frequently used by women (53.3%). β -blockers, diuretics and other drugs were more often used by men. In turn, calcium channel blockers, had equal distribution between the genders. However, the difference between the values of the antihypertensive drug classes was not statistically significant.

The laboratory parameters from the patients in hemodialysis are depicted on Table 3. The mean post-dialysis urea value was significantly higher in men when compared to women ($p = 0.01$). Other variables, such as serum creatinine, phosphorus, potassium, calcium, albumin, hemoglobin, hematocrit and pre-dialysis urea were similar for both groups.

TABLE 3 MEAN VALUES OF THE BIOCHEMICAL AND HEMATOLOGIC MARKERS OF DIALYSIS PATIENTS BY GENDER (N = 48)

Variable	Men (N = 24)	Women (N = 24)	<i>p</i>
Serum creatinine (mg/dL)	8.2 ± 3.9	9.2 ± 3.9	0.64
Serum phosphorus (mg/dL)	6.4 ± 2	6.4 ± 1.9	0.65
Serum potassium (mEq/L)	5.8 ± 1.6	6 ± 1.6	0.99
Serum calcium (mg/dL)	8.9 ± 0.9	8.8 ± 0.9	0.67
Serum albumin (g/dL)	4.1 ± 0.5	3.9 ± 0.5	0.31
Hemoglobin (g/dL)	11.9 ± 2.1	11.5 ± 2.1	0.63
Hematocrit (%)	37.9 ± 9.6	35.4 ± 9.5	0.55
Predialysis urea (mg/dL)	140.1 ± 28.4	143.1 ± 28.4	0.82
Post-dialysis urea (mg/dL)	49.3 ± 12.1	42.4 ± 12.1	0.01

DISCUSSION

The interest in epidemiological data on ADPKD is perceived around the world. ADPKD occurs in

all ethnic groups, but there are many variations in prevalence reported in different regions:

- In North America, a study in Olmsted County,³ an isolated county in the state of Minnesota, the estimated prevalence was 1 in 1,000 live births (only clinically diagnosed) and 1 in 400 when the autopsy cases were included. Another study conducted in Tennessee and Georgia,²⁵ found a similar prevalence for blacks and whites (0.48 and 0.47 per 100,000, respectively);
- In Europe, the prevalence is lower, as per shown in a study conducted in France,²⁶ which found a prevalence of 90 per 100,000 inhabitants (or 1:1.111), in the UK,²⁷ more specifically in Wales, is 41 per 100,000 (or 1:2.459); in southern Portugal,²⁸ more specifically in Alentejo, the prevalence is 33.1 per 100,000 inhabitants (or 1:3.019);
- In Japan,¹⁹ one study reported a prevalence of 25 per 100,000 inhabitants (or 1:4.033);
- In Africa, data is scarce. In Senegal,²⁹ a ten-year retrospective study involving 55 patients reported a prevalence of one in 250; in Seychelles,³⁰ an island in the Indian Ocean, one population-based study found 65% of people of African descent and 30% mixed or Euro-descendants and found a prevalence in African and Caucasian populations of 2 and 184 per 100,000, respectively (or 1:544), increasing to 6 and 236 per 100,000 inhabitants aged 25-39 years.

In the present study, we evaluated the frequency of patients with ADPKD in hemodialysis from four dialysis centers in a state in southern Brazil. Polycystic kidneys were observed in 10.3% of the patients with stage 5 CKD and the prevalence was 9.2 per 100,000 inhabitants (or 1:10.912). In the studies published to date, we did not find a prevalence similar to the one found in this study, especially in the Brazilian studies available. A prevalence closest to these findings was found in a study in Galicia,³¹ in Spain, which reported one case for every 8,132 inhabitants.

Male patients diagnosed with ADPKD begin dialysis earlier than women.^{5,32,33} The mean age at

which men start dialysis (50.7 years) was lower than that of women (51.6 years) in this study, which although not statistically significant, corroborates this statement. Studies carried out with different populations¹¹ yielded similar data, indicating the average age of initiation of renal replacement therapy lower in men, without however reporting significant differences between genders. However, a study carried out in Spain,¹⁵ despite finding higher mean ages at onset of dialysis than ours, reported an age similarity between men and women with 57.2 and 57.7 years, respectively.

The male gender is a determining factor in the progression of ADPKD for worse outcomes, which leads men to require more early kidney transplant because of these and other risk factors related to gender, such as diagnosis in those under 30 years of age, kidney enlargement and hormonal influence.^{5,34} Therefore, the present study found a shorter follow-up on dialysis until transplantation in men (36.5 months) compared to women (39.8 months), although there were no significant differences. A previous Brazilian study involving 132 patients with ADPKD reported an even shorter time of 25.2 months; however, without distinction between genders.¹³ Another retrospective study conducted in Spain reported a longer average stay on dialysis until transplantation - 41 months, with no distinction between genders.¹⁵ In studies published to date, there were no gender differences in the dialysis follow-up time until transplantation for ADPKD patients, making the data from this study difficult to compare.

Hypertension is one of the early signs of ADPKD and is present in over 50% of patients with the disease and in 80% of those in dialysis.^{12,35} In this study, hypertension was presented as the most frequent renal manifestation in 73% of ADPKD patients, with a female predominance (51.4%) over males, although there were no significant differences between genders. These findings were confirmed by a Brazilian study involving 92 patients with polycystic kidneys, which found a slightly higher frequency of hypertension among females (70.5%); however, in contrast to the results

of this study, they reported differences between the genders.¹¹ On the other hand, several retrospective studies involving populations with ADPKD have described hypertension as the most common renal disease in humans, with significant differences between the genders.^{5,24} Another study involving 53 patients in the city of Dakar, in Africa, also reported hypertension as the predominant renal manifestation in men - 61.1% of the cases, despite not finding differences between the genders.²⁹ These differences can be explained by the fact that in such study, the women were older than the men, which may increase the influence of female hormones on blood pressure, especially in women over 55 years, leading to hypertension. In addition, other risk factors not described in this study, such as smoking and obesity, may be involved.

Liver cyst is also a common finding among patients with ADPKD, most frequently among females.^{2,11} However, this study found liver cysts as the most frequent extra-renal manifestation in men (60.0%); however, there were no significant differences between genders. A study carried out in Salamanca, Spain, evaluated 48 patients, and among them there was an incidence of 59.1% of liver cysts in women, with significant differences between the genders.⁵ Similarly, a study in Senegal evaluated 53 African patients with ADPKD and found a frequency of 63% of liver cysts in women, with significant differences between genders.²⁹ In contrast to this study, a research conducted in São Paulo evaluated 92 patients and reported a higher frequency of liver cysts in females, with differences between the genders.¹¹ It is believed that there may have been an underestimation of the number of cysts in women because the study was retrospective, with limited access to past tests and gaps in the records filled out by the health care team.

Before 1975, the leading cause of death in patients with ADPKD was uremia. With the advent of hemodialysis, cardiovascular diseases have become the leading cause, mainly due to hypertension.³⁶ In this study we had five patients with ADPKD who died during the study period, i.e. 10.4% of all of those submitted to

dialysis - 60% of men and 40% women, with no significant differences between the genders. This higher frequency of deaths for males is supported by a retrospective study carried out in Spain with 48 patients, while highlighting a higher frequency of deaths (39.6%) of the total number of patients with polycystic kidneys in relation to this study, they found 29.2% of deaths in men and 10.4% in women, with significant differences between the genders.⁵ Another retrospective study carried out in the United States with 129 patients examined the causes of deaths in patients with polycystic kidneys in or out of kidney replacement therapy, and also found a similar incidence of deaths in males (61%), with no differences between the genders.³⁶

Several experimental and clinical studies carried out in patients with polycystic kidneys show increased activity of the renin-angiotensin-aldosterone system, whose potential adverse kidney effects of angiotensin II are suppressed by renin-angiotensin system drugs that comprise the class of antihypertensive agents most frequently used in treatment.^{17,24} In this study, RAS drugs represented the only class of antihypertensive agents with greater frequency in 53.3% of females without, however, presenting significant differences between genders. However, a retrospective epidemiological study analyzed 53 black African patients and found that the RAS drugs were used in a similar frequency among the genders.²⁹ Another longitudinal study in the United States evaluated hypertensive patients with ADPKD in two distinct cohorts and also reported a significant increase in the use of RAS drugs for both genders.³⁷

Urea is an end product of protein metabolism and builds up in the blood due to the reduction in kidney filtration. Excess urea is removed by dialysis, but this elimination is not complete.³⁸ In this study, although the mean post-dialysis urea attained was lower for both genders in relation to the initial values, it was not possible to analyze the dialysis efficiency, since the main parameters used to evaluate it (Kt/V or urea reduction ratio) were not in the majority of patients' records. However, we noticed that the average post-dialysis urea was significantly higher in males

when compared to females ($p = 0.01$), suggesting a reduced protein intake by women or just a statistical variation.^{39,40}

CONCLUSION

This is one of the first Brazilian epidemiological studies reporting the prevalence and the clinical and laboratory profiles of ADPKD by gender. The results revealed that the prevalence of ADPKD is low among patients in hemodialysis from the northwest of the state of Paraná, Brazil. In general, the clinical and laboratory profile of ADPKD by genre is different from the data reported in North America and Europe, probably due to the mixed ethnic make up of the study population.

This study had some limitations. The main one is that, despite the observational study design, data collection was retrospective and from the point of view of the analysis, it caused an underestimation of many of the clinical manifestations and, thus, it limits the association between the values of the groups. On the other hand, the study population was not large enough. However, despite the small sample size, this study is one of the first to be held in Brazil, surpassed only by isolated studies published in the literature that reinforce it.

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