

## Clinical aspects of autosomal recessive polycystic kidney disease (ARPKD)

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This study was conducted in the Pediatric Nephrology Unit of the Instituto da Criança of the Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) and LIM/29 Discipline of Nephrology. Program of Scientific Initiation of the Instituto da Criança - Fundação Faculdade de Medicina.

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### ABSTRACT

**Introduction:** Autosomal Recessive Polycystic Kidney Disease (ARPKD) is an important pediatric cause of morbidity and mortality, with a variable clinical spectrum. **Methods:** The clinical presentation and evolution of 25 patients (Pts) were analyzed by clinical record review, according to the forms proposed by Guay-Woodford *et al.* Morbidities associated with the disease were evaluated with respect to their frequencies and age of onset. **Results:** The median age at the diagnosis was 61.45 months (0 to 336.5 months), with similar gender distribution (52% of the patients were female). A family ARPKD history was found in 20% of the cases (5/25), two of them associated with consanguinity. On arrival, arterial hypertension (SAH) was diagnosed in 56% of the Pts (14/25); chronic kidney disease stage  $\geq 2$  (CKD  $\geq 2$ ) in 24% (6/25); urinary tract infection (UTI) in 40% (10/25); and portal hypertension (PH) in 32% of the cases (8/25). Eighty percent of the initial abdominal ultrasonograms detected echogenic kidneys with gross cysts and 64% demonstrated normal liver and biliary ducts. ACE inhibitors were used in 36% of the analyzed patients, beta-blockers in 20%, calcium channel blockers in 28%, and diuretics in 36% of them. In the final evaluation, after an average follow-up time of 152.2 months (29.8 to 274.9 months), SAH was detected in 76% of the cases, CKD  $\geq 2$  in 44%, UTI in 52% and PH in 68%. **Conclusion:** The high morbidity and mortality associated with ARPKD justify the assembly of an international database, with the aim of establishing an early therapeutic support.

**Keywords:** autosomal recessive polycystic kidney; database; pathologic processes.

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### INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD) is a frequently severe form of pediatric cystic kidney disease that affects the kidneys and the biliary tract. It has an estimated incidence of approximately 1:20,000 live births, as suggested in the most recent analyses by Zerres *et al.*<sup>1</sup>

All typical forms of ARPKD result from mutations in the same gene, PKHD1 (Polycystic Kidney and Hepatic Disease 1). That *locus* was mapped to the chromosome 6p21.1-p12 in 1994/1995<sup>2,3</sup> and identified by Onuchic *et al.* and Ward *et al.* in 2002.<sup>4,5</sup> The first group of researchers used positional cloning, while the other group of researchers used the characterization of that gene's ortholog, mutated in the model of the PCK rat. The PKHD1 gene extends over a genomic segment of at least 469 kb and is highly complex, comprising a minimum of 86 exons. Its exons are assembled in a complicated pattern of splicing, originating a large number of alternative transcripts.<sup>4</sup>

PKHD1 encodes an integral membrane protein with 4,074 amino acids and still poorly known function, called polyductin or fibrocystin.<sup>4,5</sup> However, if many of its alternative transcripts are translated, the proteins encoded by that gene should form two groups: one comprising transmembrane domain products, related to the membrane, and other including proteins without that domain and, therefore, soluble and possibly secreted. Several authors have recently assessed the expression profile of polyductin. In the adult human kidney, its expression has been detected in the cortical and medullary collecting tubules and in the thick ascending limb of Henle's loop.<sup>6</sup> On the other hand, at the

subcellular level, expression of polyductin in the axoneme and basal body of primary apical *cilia* has been demonstrated, indicating that it is one more protein involved in the pathogenesis of a polycystic kidney disease expressed in that organelle.<sup>6</sup> Positive labeling in the luminal membrane and cytoplasm of the cells of the collecting duct has also been detected. Those studies have also included embryonal kidney tissue of mouse, showing specific labeling in the branch of the ureteric bud.

The diagnosis of ARPKD can be performed in the intrauterine period, neonatal period or in the first months of life, through ultrasound detection of bilateral diffuse kidney enlargement. Its clinical presentation, however, is highly variable and can be identified in the perinatal, infantile, or juvenile period. Oligohydramnios is a common finding, due to the low fetal urinary output, and is rarely observed before the 20<sup>th</sup> gestational week. As a consequence of the oligohydramnios, the fetuses affected develop the Potter sequence, a phenotype comprising lung hypoplasia, typical facies, and extremity anomalies. Regarding histopathology, ARPKD is characterized by a fusiform dilatation of the collecting tubules and dysgenesis of the hepatic portal triad - characterized by hyperplastic biliary ducts and congenital hepatic fibrosis.

Recessive autosomal polycystic kidney disease has a poor prognosis, and approximately 30% of the neonates affected die in the perinatal period, usually as a result of respiratory failure. Less severe cases survive and have bilaterally palpable kidneys, arterial hypertension, impaired urine concentration, metabolic acidosis due to impaired distal acidification, and progressive kidney failure. Liver impairment varies and can be asymptomatic or progress to portal hypertension.

Bergmann *et al.* have shown that most mutations are unique within a family (*private mutations*), making the establishment of genotype-phenotype correlations difficult and complicating the elaboration of a direct test for molecular diagnosis.<sup>7</sup> On the other hand, genotype-phenotype correlations have been mainly based on the type of mutation. Almost all patients with both mutations associated with the truncation of the longest open reading frame product of the gene have the most severe phenotype of the disease, while almost all patients with a moderate phenotype have at least one mutation associated with the replacement of amino acids in polypeptide chains.<sup>8,9,10</sup> The mutation most frequently found in the studies performed to this date was c.107 C > T, a missense mutation. The greatest mutation detection rate obtained

so far, 87.5%, was achieved by Sharp *et al.* in a study using the strategy of denaturing high performance liquid chromatography (DHPLC) and sequencing.<sup>10</sup>

The present study aimed at assessing the initial and follow-up clinical data of patients diagnosed with ARPKD and followed up at the outpatient clinic of the Unit of Pediatric Nephrology of the *Instituto da Criança* - HCFMUSP. That assessment was performed by use of initial and follow-up clinical questionnaires developed by Guay Woodford *et al.* for characterizing North-American patients.<sup>11</sup> Such information will be essential for the clinical characterization of ARPKD and its understanding, as well as for establishing genotype-phenotype correlations.

## PATIENTS AND METHODS

The medical records of patients diagnosed with ARPKD were retrospectively assessed. Such patients had been registered at the *Instituto da Criança* - HCFMUSP, from 1990 to July 2008. Their diagnosis was based on the criteria of initial and follow-up clinical history based on the questionnaire developed by Guay-Woodford *et al.*<sup>11</sup> The guardians of all patients whose medical records were assessed provided written informed consent for their participation in the study, and the study project was submitted to and approved by the Committee on Ethics and Research of the HCFMUSP.

The data obtained underwent a descriptive statistical analysis by using mean (or median), maximum, and minimum values for continuous variables and frequencies for categorical variables.

## RESULTS

### DESCRIPTION OF THE COHORT AND DEMOGRAPHIC CHARACTERISTICS

The assessment of the patients of the Unit of Nephrology of the *Instituto da Criança* - HCFMUSP diagnosed with ARPKD was conducted by using a database of SAME, in the period from 1990 to 2008. Of the 98 patients initially listed, 25 had their diagnosis of ARPKD confirmed. Then, each medical record was assessed, and the admission and follow-up forms of each patient were all completed.

The distribution of the disease was similar between genders, with 13 (52%) female patients and 12 (48%) male patients. The ethnicity mostly affected by ARPKD was Caucasian (76%), followed by African (20%) and Asian (4%; 1 patient). Prenatal diagnosis was established in 5 cases (20%), by use of fetal ultrasound scan. Consanguinity between parents

was evidenced in only two cases and family history of ARPKD in five (20% of the cases). Two patients died because of septicemia due to dialysis complications.

### CLINICAL CHARACTERISTICS

The mean age at diagnosis was 61.45 months (0 to 336.5 months).

Regarding the gestational age, four cases were premature (16%), 13 cases were full term (52%), while in the remaining eight cases (32%) no information was provided. Neonatal mechanical ventilation was required in two premature newborns (50%) and one full-term patient (5%), but none of them developed chronic pneumopathy.

Table 1 shows the frequencies of identification of the clinical characteristics upon diagnosis and final analysis of the cases, after a mean follow-up of 152.2 months (29.8 to 274.9 months).

To control arterial hypertension diagnosed upon presentation, 36% of the patients used angiotensin-converting enzyme inhibitors (ACEI); 20% used beta-blockers; 28% used calcium-channel blockers; and 36% used diuretics. Recombinant human erythropoietin was introduced upon presentation in 8% of the cases for the treatment of anemia secondary to chronic kidney failure. By the time of final assessment, 68% of the patients had used ACEI to control arterial hypertension (17/25), 44% had used beta-blockers (11/25), 48% had used calcium channel blockers (12/25), and 36% had used diuretics (9/25). Recombinant erythropoietin was administered to 20% of the patients (5/25) to treat anemia associated with chronic kidney disease.

### RADIOLOGIC FINDINGS

Initial radiologic assessment revealed, in 80% (20/25) of the kidney ultrasound scans, echogenic kidneys with gross cysts, while only 40% of the ultrasound scans with no gross cysts (2/5) showed an increase in kidney size. Liver ultrasound scan was normal in 64% of the patients (16/25), while 28% of the patients (7/25) had echogenic liver, and 16% (4/25) had dilated biliary ducts.

### HISTOPATHOLOGICAL FINDINGS

Two patients underwent unilateral nephrectomy prior to dialysis. The histological analysis of that material showed dilated distal and collecting tubules. Thirteen liver biopsies were performed, six of which (46.1%) revealed biliary dysgenesis and five (38.5%) showed congenital hepatic fibrosis.

### DISCUSSION

Our findings represent the beginning of the clinical study of ARPKD in Brazil. The comparison of the present study data with those from the greatest clinical database of ARPKD, representative of the North-American population<sup>11</sup>, has shown similar sex and ethnic distributions, with a mean age at diagnosis (61.45 months) much greater than that reported in the North-American cohort (1 to 72 days of life).

**Table 1**

CLINICAL CHARACTERISTICS OF ARPKD  
FREQUENCY OF IDENTIFICATION OF THE  
CLINICAL CHARACTERISTICS OF ARPKD UPON  
DIAGNOSIS AND FINAL ANALYSIS

Clinical characteristic	Frequency upon diagnosis <sup>i</sup>	Frequency upon final analysis
Arterial hypertension	56% (14/25)	76% (19/25)
Urinary infection	40% (10/25)	52% (13/25)
Hyponatremia	16% (4/25)	–
Renal lithiasis	4% (1/25)	4% (1/25)
Chronic kidney failure (CKF)	24% (6/25)	44% (11/25)
CKD stage 5	8% (2/25)	12% (3/25)
Kidney transplantation	–	4% (1/25)
Portal hypertension	32% (8/25)	68% (17/25)
Bleeding esophageal varices		16% (4/25)
24% (6/25)		
Hypersplenism	4% (1/25)	28% (7/25)
Cholangitis	–	5% (1/25)
Recurrent abdominal pain	12% (3/25)	8% (2/25)
Growth delay	20% (5/25)	24% (6/25)

CKD = chronic kidney disease.

In our cases, 20% of the diagnoses were antenatal, a figure greater than that reported by Zerres *et al.*<sup>1</sup> in the German population (10%), but much lower than that of the North-American cohort, in which 45.8% of the live births after 1990 had a prenatal diagnosis of ARPKD. In our study, neonatal mechanical ventilation was required in 2/4 of the premature newborns (50%) and in one full-term patient (5%), but none of them developed chronic pneumopathy. On the other hand, in the above-cited North-American cohort, 40% of births after 1990 required mechanical ventilation, and 11.6% developed chronic pneumopathy.

Portal hypertension was diagnosed in 68.0% of our patients in the follow-up period, while only 34.2% of the North-American patients had it. The frequency of bleeding esophageal varices was also increased in the Brazilian group of patients (24.0%) as compared to that of the North-American patients (10.0%).

Regarding the initial finding of hyponatremia, our data are similar to those of the North-American patients. The same was observed regarding the frequencies of chronic kidney failure and arterial hypertension, the latter being the most frequently diagnosed morbidity in ARPKD. The frequencies of kidney and liver transplantations reported by Guay-Woodford *et al.*<sup>11</sup> were 22.5% and 7.0%, respectively, while in our population of patients, 5.0% underwent kidney transplantation and none underwent liver transplantation.

The ultrasound findings in the North-American study<sup>11</sup> revealed echogenic kidneys with gross cysts in 50.0% of the initial ultrasound scans and echogenic kidneys without cysts in the remaining cases. Regarding the initial liver ultrasound scans, 52.7% were within the normal range. On the other hand, our findings showed echogenic kidneys with gross cysts in 80.0% of the initial kidney ultrasound scans (20/25) and a normal pattern in 64.0% of liver ultrasound scans. However, it is worth emphasizing that, according to Zerres *et al.*<sup>1</sup>, ultrasound alterations frequently pass unnoticed in the prenatal period, the time when almost half of the North-American ARPKD cases are diagnosed.

The histopathological findings of the kidneys in both group of patients were similar. However, in the North-American group, biliary dysgenesis was found in 95.5% of the patients, while in the Brazilian group, 46.1% of the patients had biliary dysgenesis, 38.5% had congenital hepatic fibrosis, and 15.4% showed unaltered hepatic morphology.

## CONCLUSION

In conclusion, our findings show the varied manifestations of ARPKD in the Brazilian population. The patients studied were diagnosed at a late stage, which was complicated by the frequent lack of knowledge about the clinical presentation of ARPKD of the health professionals in our country. Such patients usually had early kidney impairment with subsequent development of liver morbidities.

Our findings represent the beginning of a project aimed at building a database with demographic and initial and follow-up clinical characteristics of ARPKD in the Brazilian population to collect the information needed to establish genotype-phenotype correlations. The next step is the already initiated aggregation of patients from other medical centers from several regions of Brazil. The importance of a national database lies not only on the characterization of

the disease in the Brazilian population, but also on the feasibility of the identification of patients for future clinical studies.

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