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Clinical Characteristics and Courses of Patients With Autosomal Recessive Polycystic Kidney Disease-Mimicking Phenocopies

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INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD) is a rare genetic fibrocystic disorder of kidneys and liver, primarily caused by biallelic variants in the *PKHD1* gene.[1] Variants in multiple genes can result in ARPKD-mimicking phenocopies, including genes causing autosomal dominant polycystic kidney disease (ADPKD), *HNF1B*-nephropathy, or nephronophthisis.[2] Clinical differentiation between ARPKD and ARPKD-mimicking phenocopies like severe very early-onset forms of ADPKD, *HNF1B*-related cystic kidney disease, or nephronophthisis may be difficult.[1,3] ADPKD is mainly caused by variants in *PKD1* or *PKD2*.[1]

Retrospective long-term follow-up of a large cohort of patients with very early-onset forms of ADPKD showed better kidney-related outcomes in adolescence than in children with ARPKD but children of this cohort did not necessarily show an initial ARPKD-like phenotype.[4] *HNF1B*-related nephropathy has been associated with slowly progressing functional kidney impairment in most patients.[5] Prognosis of nephronophthisis varies according to the underlying genetics.[6]

Here, we describe the clinical follow-up of well-described patients with the clinical diagnosis of ARPKD that were subsequently genetically diagnosed to suffer from another cystic kidney disease and were thus classified as phenocopies.

RESULTS

Patient Inclusion

From a total of 665 patients clinically diagnosed in the ARPKD registry study ARegPKD, we identified a subset

of 243 patients with relevant *PKHD1* variants (≥1 *PKHD1* variant of unknown significance, likely pathogenic, or pathogenic variant). We also identified 31 patients without detected *PKHD1* variants but with subsequent identification of variants in other genes known to be associated with cystic kidney disease as the most likely disease cause (Figure 1a). Variants in *PKD1* were detected in 17 of 31 patients (54.8%) including 3 patients carrying 2 variants in *PKD1* and 1 patient carrying 1 additional *PKD2* variant. Fourteen patients did not carry variants in *PKD1*. Variants in *HNF1B* and *TMEM67* were detected in 5 patients each and variants in *PKD2* and *NPHP3* in 2 patients each. The patient carrying variants in *PKD1* (heterozygous) and *PKD2* (heterozygous) was included in the *PKD1* subgroup for further analyses (Figure 1b). Patient characteristics are presented in Table 1 and Supplementary Tables S1, S2.

Prenatal and Perinatal Clinical Characteristics and Symptoms at Diagnosis

Almost 60% of all patients with ARPKD phenocopies showed prenatal sonographic anomalies (Table 1). Nine patients with phenocopies (32.1%) suffered from prenatal oligohydramnios or anhydramnios. One patient carrying a heterozygous frameshift variant in *PKD1* received amnioinfusions, required early dialysis, and died in the first year of life. One patient had intestinal atresia. Patients with *PKD1* phenocopies seemed to be affected more frequently by perinatal problems than patients without *PKD1* phenocopies.

Frequent initial postnatal symptoms were distended abdomen, palpable mass/tumor with enlarged kidneys, and bilateral renal cysts. Reported arterial hypertension was a predominant symptom in patients with *PKHD1*-related ARPKD and *PKD1* phenocopies.

Liver manifestation with radiological signs of hepatic fibrosis at diagnosis was detected in 30.4% of patients with *PKHD1* variants, but only 14.3% of patients with non-*PKD1* and 12.5% of patients with *PKD1* phenocopies.

Clinical Follow-up of Kidney Disease

Overall, Kaplan-Meier event-free follow-up without kidney replacement therapy (KRT; dialysis or

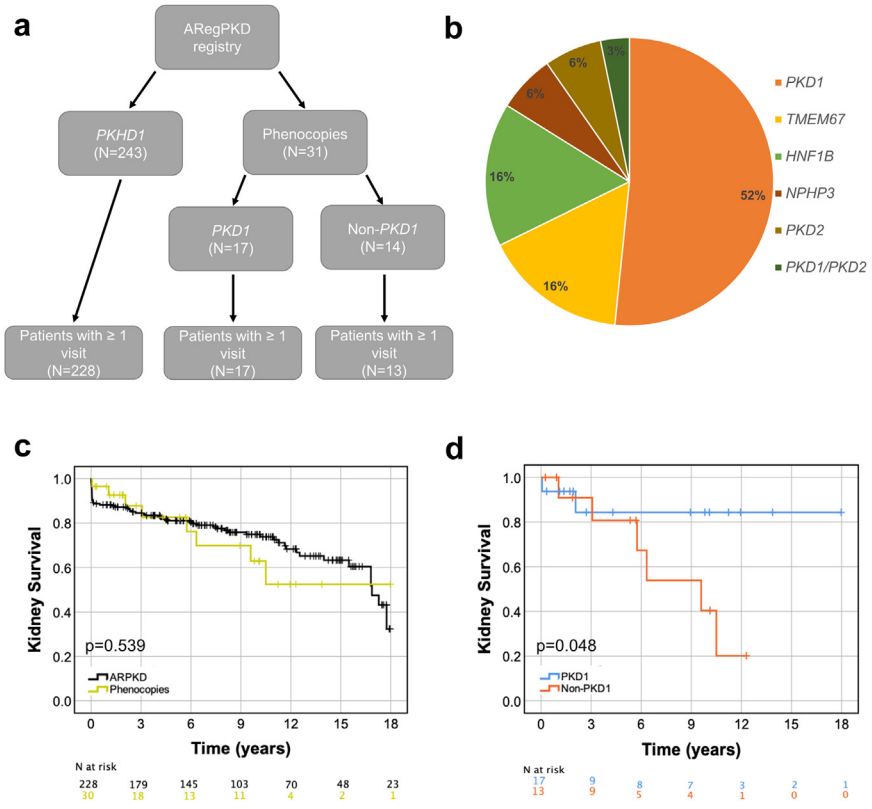

Figure 1. (a) Flow chart of ARPKD phenocopy selection process. Within the registry data, 243 patients with an ARPKD phenotype and at least 1 relevant *PKHD1* variant were identified, 228 of which had follow-up information from ≥1 visit. In 31 patients without *PKHD1* variants, relevant variants in other cystic kidney disease genes were identified, 30 of which had follow-up information from ≥1 visit. (b) Pie chart of genes with rounded percentages of detected variants in 31 patients with ARPKD phenocopies. More than half ($n = 16$, about 52%) of these patients with detected variants had variants in *PKD1*. One additional patient (3%) had variants in both *PKD1* and *PKD2*. Further analyses revealed variants in *TMEM67* and *HNF1B*, in about 16% of the patients ($n = 5$) in each phenocopy gene. In 6% of patients ($n = 2$) each, variants were detected in *NPHP3* as well as in *PKD2*. (c) Kaplan-Meier curve for kidney survival in patients with *PKHD1*-related ARPKD vs. patients with phenocopies. (d) Kaplan-Meier curve for kidney survival in subcohorts of patients with *PKD1* vs. non-*PKD1* phenocopies. The event was defined by start of kidney replacement therapy or death. Censored observations (last documented follow-up) are marked with a tick. Log rank *P*-value is indicated for the entire observation period.

Table 1. Patient characteristics and clinical characteristics of the cohort

Patient charecteristics	All patients with phenocopies (total n = 31)			Patients with *PKHD1*-related ARPKD (total n = 243)
Gender (male), n (%)	12/31 (38.7%)			128/243 (52.7%)
Age at diagnosis, yrs				
Age at diagnosis, n	29			227
Median (IQR)	0.1 (0.0–1.1)			0.3 (0.1–1.6)
Age at first visit, yrs				
Age at first visit, n	30			228
Median (IQR)	1.4 (0.1–7.9)			1.2 (0.2–6.6)
Age at last visit, yrs				
Age at last visit, n	30			228
Median (IQR)	7.4 (1.8–13.0)			10.0 (5.5–15.8)
Follow-up time, yrs				
Follow-up time, n	23			197
Median (IQR)	2.1 (1.3–5.4)			6.0 (3.4–10.8)
Clinical characteristics	**All patients with phenocopies (total *n* = 31)**	***PKD1* subcohort (total *n* = 17)**	**non-*PKD1* subcohort (total *n* = 14)**	**Patients with *PKHD1*-related ARPKD (total *n* = 243)**
Prenatal information				
Prenatal abnormalities, n (%)	18/30 (60.0%)	10/16 (62.5%)	8/14 (57.1%)	108/217 (49.8%)
Oligo- or anhydramnios, n (%)	9/28 (32.1%)	6/16 (37.5%)	3/12 (25.0%)	80/206 (38.8%)
Gestational age at diagnosis in wks, n	8	5	3	75
Median (IQR or min;max)	29.5 (21.0–35.8)	30.0 (18.0–37.0)	29.0 (24.0;35.0)	30.0 (27.0–34.0)
Increased echogenicity, n (%)	12/25 (48.0%)	7/14 (50.0%)	5/11 (45.5%)	42/182 (23.1%)
Gestational age at diagnosis in wks, n	11	7	4	40
Median (IQR)	24.0 (20.0–30.0)	20.0 (20.0–34.0)	26.5 (24.0–30.0)	29.5 (26.3– 33.8)
Renal hyperplasia, n (%)	11/26 (42.3%)	6/14 (42.9%)	5/12 (41.7%)	46/193 (23.8%)
Renal cysts, n (%)	11/26 (42.3%)	6/14 (42.9%)	5/12 (41.7%)	41/193 (21.2%)
Amnioinfusion	1/30 (3.3%)	1/17 (5.9%)	0/14 (0%)	6/209 (2.9%)
Perinatal information				
Normal delivery, n (%)	11/30 (36.7%)	6/17 (35.3%)	5/13 (38.5%)	111/192 (57.8%)
Gestational age at birth in wks, n	28	14	14	173
Median (IQR)	38.0 (37.0-39.8)	38.0 (36.0-40.0)	38.5 (37.0-39.3)	37.0 (35.0-39.0)
Perinatal Problems, n (%)	14/31 (45.2%)	8/17 (47.1%)	6/14 (42.9%)	84/215 (39.1%)
NICU, n (%)	7/30 (23.3%)	5/17 (29.4%)	2/13 (15.4%)	65/210 (31.0%)
Days on NICU, n	6	5	1	59
Median (IQR or min;max)	21.5 (11.3–46.5)	25.0 (10.5–63.0)	14.0 (14.0;14.0)	21.0 (9.0–25.0)
Poor postnatal adaptation, n (%)	8/31 (25.8%)	6/17 (35.3%)	2/14 (14.3%)	59/211 (28.0%)
Assisted breathing or ventilation, n (%)	6/30 (20.0%)	5/17 (29.4%)	1/13 (7.7%)	58/210 (27.6%)
Pulmonary hypertension, n (%)	3/29 (10.3%)	3/16 (18.8%)	0/13 (0%)	18/198 (9.1%)
Potter facies, n (%)	2/29 (6.9%)	1/16 (6.3%)	1/13 (7.7%)	8/205 (3.9%)
Postnatal information				
Birth weight in kg, n	29	15	14	179
Median (IQR)	3.16 (2.67–3.56)	3.20 (2.65–3.70)	3.07 (2.64–3.46)	3.03 (2.58–3.33)
Birth length in cm, n	27	13	14	137
Median (IQR)	51.0 (49.0–54.0)	51.0 (47.3–53.5)	50.0 (48.3–56.3)	49.0 (46.0–52.0)
Apgar 1, n	26	14	12	120
Median (IQR)	8.0 (7.8–9.0)	8.5 (7.5–9.3)	8.0 (7.3– 9.0)	8.0 (6.0–9.0)
Apgar 5, n	26	14	12	120
Median (IQR)	9.0 (8.8–10.0)	10.0 (8.5–10.0)	9.0 (8.3–9.8)	8.0 (7.0–10.0)
Apgar 10, n	23	12	11	120
Median (IQR)	10.0 (9.0–10.0)	10.0 (9.3–10.0)	10.0 (8.0–10.0)	9.0 (8.0–10.0)
Initial symptoms leading to diagnostic workup				
Distended abdomen, n (%)	17/31 (54.8%)	11/17 (64.7%)	6/14 (42.9%)	98/212 (46.2%)
Palpable mass, n (%)	11/29 (37.9%)	10/17 (58.8%)	1/12 (8.3%)	64/206 (31.1%)
Arterial hypertension, n (%)	15/30 (50.0%)	10/17 (58.8%)	5/13 (38.5%)	118/223 (52.9%)
Failure to thrive, n (%)	10/31 (32.3%)	6/17 (35.3%)	4/14 (28.6%)	42/212 (19.8%)
Polyuria, n (%)	4/31 (12.9%)	2/17 (11.8%)	2/14 (14.3%)	5/203 (2.5%)
Polydipsia, n (%)	4/31 (12.9%)	2/17 (11.8%)	2/14 (14.3%)	5/203 (2.5%)
Recurrent pulmonary infections, n (%)	5/31 (16.1%)	2/17 (11.8%)	3/14 (21.4%)	13/218 (6.0%)
Urinary tract infection, n (%)	6/30 (20.0%)	3/17 (17.6%)	3/13 (23.1%)	44/221 (19.9%)

(Continued on following page)

Table 1. (Continued) Patient characteristics and clinical characteristics of the cohort

Clinical characteristics	All patients with phenocopies (total $n = 31$)	*PKD1* subcohort (total $n = 17$)	non-*PKD1* subcohort (total $n = 14$)	Patients with *PKHD1*-related ARPKD (total $n = 243$)
Radiological findings guiding to diagnosis				
Bilateral renal cysts, n (%)	30/31 (96.8%)	17/17 (100%)	13/14 (92.9%)	191/227 (84.1%)
"SAP" appearance on ultrasound, n (%)	8/18 (44.4%)	7/10 (70.0%)	1/8 (12.5%)	116/160 (72.5%)
Enlarged kidneys, n (%)	26/28 (92.9%)	15/15 (100%)	11/13 (84.6%)	212/227 (93.4%)
Radiological signs of hepatic fibrosis, n (%)	4/30 (13.3%)	2/16 (12.5%)	2/14 (14.3%)	63/207 (30.4%)

NICU, neonatal intensive care unit; "SAP," salt and pepper.
Number of informative cases varied by item. Binary or categorical values provided as n/total (percentage); continuous variables as median (IQR or min; max) with min; max used for cases n ≤ 3; Age at first and last visits were calculated for patients with ≥ 1 visits, if only one visit was documented then age of first visit is equal to age of last visit.

transplantation) or death was similar in patients with ARPKD phenocopies compared to patients with *PKHD1* variants (log rank $P = 0.539$; Figure 1c). Among patients with phenocopies, survival without KRT or death was better in patients of the *PKD1* subcohort compared to patients of the non-*PKD1* subcohort (10-year survival 85% in *PKD1* subcohort [$n = 17$]), 47% in non-*PKD1* subcohort [$n = 13$]; log rank $P = 0.048$; Figure 1d).

Patients with *PKD1* variants showed higher height-adjusted pole-to-pole lengths than patients of the non-*PKD1* subcohort ($P < 0.01$; Supplementary Figure S1). Beyond 1.0 years of age, an average height-adjusted pole-to-pole length of more than 10 cm/m was detected only in phenocopy patients with *PKD1* variants.

In total, 8 of 30 (26.7%) patients with ARPKD phenocopies with documented visits started KRT at a median (interquartile range) age of 5.5 (1.6–10.2) years. Out of these, 2 patients carried heterozygous variants in *PKD1*, 2 patients carried homozygous variants in *NPHP3*, and 4 patients carried homozygous or compound heterozygous variants in *TMEM67*. The patients with phenocopies carrying *PKD1* variants started KRT right after birth and at 2 years of age. The patients with phenocopies carrying *NPHP3* variants started KRT at about 1 and 3 years. Four patients carrying *TMEM67* variants initiated KRT at a median (interquartile range) age of 8.0 (5.9–10.3) years. The fifth patient with *TMEM67* variants was only followed-up until the end of the first year of life.

DISCUSSION

Clinical diagnosis of cystic kidney disease can be challenging, especially very early in life and if no extrarenal phenotypes are present. Accurate diagnosis can impact treatment and counseling of families. Overlapping phenotypes of ARPKD and other cystic kidney diseases have been described, but clinical follow-up data of ARPKD phenocopies remain scarce. In our study, a total of 31 patients with an initial clinical ARPKD diagnosis were secondarily considered to have another genetic cystic kidney disease (5% of overall cohort; 11% of patients with identified genetic variants). In more than half of these patients, variants were revealed in the *PKD1* gene, which led us to further categorize patients into *PKD1* and non-*PKD1* subgroups. Interestingly, we only witnessed subtle clinical differences between the different subcohorts. Perinatal and early postnatal problems were rather similar between *PKD1* and *PKHD1* patients in our subcohort analyses. Family history was unremarkable for cystic kidneys in our patients with very early-onset forms of ADPKD even though we detected many likely pathogenic or pathogenic variants. The 10-year kidney survival of the *PKHD1* cohort and the overall phenocopy cohort were similar. However, as previously reported,[7] event-free follow-up without KRT or death in patients with ARPKD drops steeply postnatally with a constant decrease afterwards and a 10-year survival of 75%, whereas patients with phenocopies showed a constant progression to KRT.

The non-*PKD1* subgroup of patients with ARPKD phenocopies showed similar prenatal, but fewer perinatal and postnatal anomalies than patients with *PKD1* variant. In our analysis, patients with *PKD1* variants also showed higher height-adjusted pole-to-pole lengths than patients with non-*PKD1* variants.

Interestingly, the pronounced phenotype of patients with *PKD1* variants in prenatal, perinatal, and postnatal phases does not stringently translate into worse kidney survival in the following years. Ten-year kidney survival was better in patients with *PKD1* variant than in patients with non-*PKD1* phenocopies. The inferior kidney survival in 13 patients with non-*PKD1* phenocopies can be attributed to 4 patients with *TMEM67* variants and 2 patients with *NPHP3* variants. Patients with *TMEM67* variants who require KRT in our cohort displayed cystic kidney disease with neurologic findings during follow-up.

We identified 3 patients with 2 *PKD1* variants, 1 patient carrying 2 variants in the *PKD2* gene, and 1 patient carrying 1 heterozygous *PKD1* and 1

heterozygous *PKD2* variant, which is consistent with previous studies on very early-onset forms of ADPKD.[8,9] In patients without a detected second variant, the causes of the neonatal onset of ADPKD could be numerous and could include unknown additional genetic modifiers or genetic (somatic) or clinical "second hits." It is obvious, that the classification we applied here (*PKD1* vs. non-*PKD1*) can only be helpful for a first and broad stratification.

The current study faces a number of limitations as follows: number of informative cases per item, follow-up periods, approaches to genetic testing, as well as time points and strategies of genetic testing vary. Because genetic testing is not covered in all health care systems, genetic analysis was only performed in about 55% of patients initially included in this data set. We therefore chose the subcohort of 243 patients with detected *PKHD1* variants as a control group instead of the overall cohort. Information about analyzed genes, segregation of genotypes, or copy number variation analysis was also limited. Therefore, in some cases we cannot determine whether 2 detected variants were biallelic. Other ciliopathy genes known to modulate or aggravate the phenotype were not systematically tested in our study. The pathogenicity of some variant of unknown significance findings in our cohort remains unproven. For some patients classified to the *PKD1* subcohort in the presence of a variant of unknown significance but without full examination of additional ciliopathy genes, we cannot exclude that pathogenic variants in other genes may have been missed that would have affected classification. Additional data from other cohorts or functional analyses of the specific variants will be required to further evaluate the pathogenic relevance of the associations of variant of unknown significance findings described in our study.

In summary, we present longitudinal clinical data on patients with ARPKD phenocopies. The data support the use of an next-generation sequencing-based genetic diagnostic approach to examine patients with an ARPKD-like phenotype. The exact knowledge of the underlying genotype (*PKD1* vs. non-*PKD1*) bears significant midterm to long-term prognostic value.

DISCLOSURE

Representing the University Hospital of Cologne, MCL has been counseling Otsuka on an advisory board. The other authors declared no conflicting interest.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Scatterplot of the height-adjusted average pole-to-pole (haAvPTP) length of the kidneys in 19 phenocopy patients, 12 *PKD1* and 7 non-*PKD1*.

Table S1. Distribution of countries of origin of parents.

Table S2. Genetic variants detected.

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