Risk Factors for Early Dialysis Dependency in Autosomal Recessive Polycystic Kidney Disease

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Objective To identify prenatal, perinatal, and postnatal risk factors for dialysis within the first year of life in children with autosomal recessive polycystic kidney disease (ARPKD) as a basis for parental counseling after prenatal and perinatal diagnosis.

Study design A dataset comprising 385 patients from the AReg PKD international registry study was analyzed for potential risk markers for dialysis during the first year of life.

Results Thirty-six out of 385 children (9.4%) commenced dialysis in the first year of life. According to multivariable Cox regression analysis, the presence of oligohydramnios or anhydramnios, prenatal kidney enlargement, a low Apgar score, and the need for postnatal breathing support were independently associated with an increased hazard ratio for requiring dialysis within the first year of life. The increased risk associated with Apgar score and perinatal assisted breathing was time-dependent and vanished after 5 and 8 months of life, respectively. The predicted probabilities for early dialysis varied from 1.5% (95% CI, 0.5%-4.1%) for patients with ARPKD with no prenatal sonographic abnormalities to 32.3% (95% CI, 22.2%-44.5%) in cases of documented oligohydramnios or anhydramnios, renal cysts, and enlarged kidneys.

Conclusions This study, which identified risk factors associated with onset of dialysis in ARPKD in the first year of life, may be helpful in prenatal parental counseling in cases of suspected ARPKD. *(J Pediatr 2018;■■:■■-■■).*

Autosomal recessive polycystic kidney disease (ARPKD) is a rare but severe early-onset ciliopathy mainly caused by mutations in the *PKHD1* gene.[1-3] Mutations in *DZIPL1* also have been described in 4 unrelated families.[4] The disease results in loss of renal function in ~50% of patients within the first 2 decades of life.[5] Despite the low incidence (1:20 000 live births), ARPKD is a major cause of end-stage renal disease necessitating renal replacement therapy in early childhood.

ARPKD has a broad phenotypic spectrum, both across and within affected families. Whereas some patients show a minimal kidney phenotype but pronounced hepatic pathology, others have intrauterine oligohydramnios, subsequent pulmonary hypoplasia, and early renal failure.[6] Both prenatal parental counseling and immediate postnatal decision making are challenged by the scarcity of reported

AIC	Akaike information criterion
ARPKD	Autosomal recessive polycystic kidney disease
AUC	Area under the curve
CVVH	Continuous venovenous hemofiltration
PD	Peritoneal dialysis

Detailed affiliations available at www.jpeds.com (**Appendix 1**).

*Lists of additional members of the ESCAPE Study Group and GPN Study Group for the AReg PKD consortium are available at www.jpeds.com (**Appendix 2**).

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natural history information, including a lack of appropriately powered risk assessments regarding early postnatal end-stage renal disease and patient survival.

The predictive value of prenatal ultrasound findings appears to be limited. Although renal enlargement and oligohydramnios are generally considered risk factors for neonatal renal failure and respiratory insufficiency, preserved kidney function is not uncommon, even in children with massive prenatal sonographic pathology. Prenatal genetic diagnostics is of limited predictive usefulness in ARPKD, because genotype–phenotype correlations in *PKHD1* disease are rather loose. The prevailing concept of biallelic truncating mutations associated with perinatal or neonatal mortality[5,7] has recently been challenged by case reports of patients surviving the neonatal period with both homozygous[8] and compound heterozygous truncating *PKHD1* mutations.[9] Furthermore, prenatal genetic diagnostics requires invasive sample collection, which carries a significant risk of complications.[10] Molecular analysis of *PKHD1* is time-consuming and complex, which may delay parental counseling.

To address the need for natural history data in ARPKD, we established the longitudinal ARegPKD registry study, which is currently following >400 patients.[11,12] Here we use the comprehensive prenatal, perinatal, and postnatal information captured in ARegPKD to identify risk factors associated with the need for renal replacement therapy in the first year of life in children with ARPKD.

Methods

Children and adults with a clinical diagnosis of ARPKD were enrolled in the international ARegPKD registry study according to clinical diagnostic criteria for ARPKD described previously.[11-13] Exclusion criteria encompass genetic, histological, or clinical proof of other cystic kidney disorders. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of Cologne University and the Institutional Review Boards of the participating sites. Subject pseudonymization is performed at the local center after written informed consent. Pseudonymized data are entered into a password-restricted, web-based database (www.aregpkd.org) by authorized medical personnel.

Both prospective and, as available, retrospective data are collected. Although visits are scheduled to be entered annually, documentation at flexible time intervals is possible. Basic data encompass age and clinical symptoms at primary manifestation as well as the perinatal period, genetic testing and family history. Prenatal and perinatal data capture includes fetal ultrasound findings ("oligohydramnios or anhydramnios", "increased renal echogenicity", enlarged kidneys indicated as "renal hyperplasia" [without quantification], "renal cysts", "other renal abnormalities", "hepatic abnormalities", "other prenatal abnormalities"), prenatal interventions (eg amnioinfusions), gestational age at birth, birth weight and length, Apgar scores, mode of delivery, admission to neonatal intensive care unit, induction of lung maturation, poor postnatal adaptation, ventilation or assisted breathing, pulmonary hypertension, Potter facies, and other abnormalities or clinical problems. All reported *PKHD1* variants were classified with regards to pathogenicity according to the revised criteria of the American College of Medical Genetics[14] and were further categorized by their putative impact on protein translation (missense vs truncating). The documentation of clinical visits encompasses a set of clinical, imaging and laboratory variables, as described previously.[11,12]

Automated checks for coherence, plausibility, and validity of the submitted information are performed according to a detailed data validation plan. Erroneous entries are recognized by application of predefined plausibility ranges for measurements, laboratory values, and medication doses. Queries are sent at regular intervals to local investigators to complete data records and solve plausibility problems or discrepancies.

Statistical Analyses

Analyses were conducted using R version 3.4.1. Percentiles and standard deviation scores of birth weight and birth height were calculated by reference to a healthy neonatal population.[15] Due to the partially retrospective data collection, data completeness varied by item. The total numbers of informative cases by item are shown in **Table I**. Data analysis was performed on the dataset available in May 2017.

Association with early onset of dialysis (within the first 12 months of life) were assessed using the χ^2 test for nominal and the Mann-Whitney *U* test for continuous variables. No formal adjustment for multiplicity was applied due to the exploratory nature of the analysis and no imputation was performed. A P value <.05 was considered significant in distinguishing between the groups.

To identify independent risk factors for dialysis during the first year of life, a multivariate Cox model was fitted. Missing values were handled via multiple imputation using chained equations (MICE algorithm).[16] In total, 20.6% of all values were imputed (see the number of informative cases in **Table I**). Partial mean matching[17] was used for continuous variables, and logistic regression modeling was used for binary outcomes. Statistical quantities (estimates, standard errors, P values) of the models were obtained from the imputed data set by aggregation via Rubin's rule.[18]

Many of the variables considered as potential risk factors are strongly correlated. To resolve issues with multicollinearity, only the single most important representative of each cluster was included in the Cox model. Here importance was assessed by comparison of the Akaike information criterion (AIC) of the respective models. Also based on assessment with the AIC, it was decided to use only the 10-minute Apgar score in the model and discard the measurements at 1 and 5 minutes. Model fit was assessed graphically via deviance residuals and revealed potential time dependencies of the coefficients for gestational age at birth, Apgar score, and assisted breathing or ventilation. This lack of fit was resolved by including simple interaction terms with time for each of these variables. Therefore, the estimated effect on the hazard ratio at any particular time t is given by the hazard ratio at time 0 (birth) multiplied

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