Clinical and pathological features of a neonate with autosomal recessive polycystic kidney disease caused by a nonsense *PKHD1* mutation

Xi-Hui Zhou, Zhi-Yan Hui, Yuan Li

Xi'an, China

Case report

Background: **Autosomal recessive polycystic kidney disease (ARPKD) is one of the most common hereditary nephropathies in childhood. We report a neonate with ARPKD presenting with oligohydramnios, enlargement and increased echogenicity of both kidneys shown by antenatal sonograms after a 29-week gestation and died within the first few hours of life.**

Methods: **The neonate was investigated pathologically post-mortem. PCR-DNA direct sequencing was performed to detect the exons of the *PKHD1* gene for mutation analysis.**

Results: **Autopsy findings of the kidney and liver confirmed the diagnostic hypothesis. *PKHD1* mutation analysis revealed that there was a homozygous nonsense mutation c.9319C>T (p.R3107X), which was found to be pathogenic, in exon 58 in the neonate.**

Conclusions: **The recurrence of *PKHD1* mutation c.9319C>T (p.R3107X) in the ARPKD population might be a good evidence that it is disease associated. Given the limitations of antenatal ultrasound, *PKHD1* mutation analysis is helpful for accurate genetic counseling and early prenatal diagnosis.**

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Author Affiliations: Department of Neonatology, the First Affiliated Hospital, Medical School of Xi an Jiaotong University/Ion Channel Disease Laboratory, Key Laboratory of Environment and Genes Related to Diseases, Ministry of Education, Xi'an 710061, China (Zhou XH, Hui ZY, Li Y)

Corresponding Author: Xi-Hui Zhou, MD, Department of Neonatology, First Affiliated Hospital, Medical College of Xi'an Jiaotong University, Xi'an 710061, China (Email: zhouxih@mail.xjtu.edu.cn)

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Introduction

Autosomal recessive polycystic kidney disease (ARPKD; MIM 263200) belongs to a group of congenital hepatorenal fibrocystic syndromes and is a significant cause of renal and liver-related morbidity and mortality in infancy and childhood.[1] ARPKD is associated with mutations in the *PKHD1* gene on chromosome 6p21. The protein that is encoded by this gene is called fibrocystin/polyductin and is involved in collecting tubule and bile duct formation, although the exact function is unknown.[2]

We present a neonate with ARPKD who died of pulmonary hypoplasia caused by oligohydramnios soon after premature birth at the gestation of 33 weeks. Autopsy findings were characterized by massively enlarged kidneys with dilated cystic collecting ducts that almost replaced the entire renal parenchyma and hypoplastic lungs. The cause of death was respiratory distress. A homozygous nonsense mutation of *PKHD1*, c.9319C>T (p.R3107X), was identified in the neonate. The parents of the neonate were heterozygous for the variant. Interestingly, the same mutation in ARPKD patients was independently shown to be pathogenic.[3]

Case report

A 33-week preterm male baby, appropriate for gestational age, was born via cesarean section because of the maternal history of oligohydramnios. The mother, gravida 2 and para 2, received no medications during pregnancy. Starting from 4 weeks before delivery, fetal sonograms showed oligohydramnios, enlarged kidneys, diffusely increased echogenicity, and loss of cortico-medullary differentiation. A presumptive diagnosis of ARPKD was made antenatally by ultrasonography. The neonate developed central cyanosis, bradycardia, and floppy posture soon after birth. Marked respiratory distress at birth led to immediate tracheal intubation. Physical examination showed an enlarged abdomen with two palpable flank masses on both sides. He was given synchronized intermittent positive pressure ventilation

(SIPPV) for respiratory support. One dose of surfactant was administered via an endotracheal tube but failed to improve oxygen saturation. Chest X-ray revealed small lung volume, poor lung expansion, and right side pneumothorax. Despite maximal respiratory support and maximum resuscitative measures, he developed progressive respiratory failure and died 9 hours after birth. No measurable urine output was recorded during his life. His mother had had a pregnancy that was diagnosed oligohydramnios by ultrasound at 27-week gestation and was then terminated. No family history of genetic diseases was found in his parents. The parents were not hypertensive. Renal ultrasound of the parents (father, 31 years old; mother, 28 years old) showed no abnormalities.

Complete autopsy was performed after informed consent was obtained from the father. Macroscopically, the kidneys were symmetrically enlarged and their reniform shape was preserved. Capsular surfaces showed multiple, minute cystic spaces, and cut surfaces showed a "spongy" appearance with no corticomedullary differentiation. Microscopically, over 90% of the renal tissue was filled with cysts (Fig. 1).

Macroscopically, small and undeveloped lungs were noted. Histologic examination revealed that alveolar spaces were collapsed and the alveolar ducts and respiratory bronchioli were dilated. The lining of the alveolar ducts was covered with fibrin-rich hyaline membranes.

Liver biopsy revealed slightly enlarged, fibrotic portal tracts and hyperplastic, dilated and dysgenetic biliary ducts. Histological examination disclosed mild periportal fibrosis with an increased number of interlobular bile ducts.

The mutation screening of *PKHD1* in the neonate revealed a homozygous cytosine to thymine nucleotide exchange in exon 58 (c.9319C>T) (Fig. 2). This variant results in a nonsense mutation of c.9319C>T (p.R3107X), suggesting a premature stop of *PKHD1* peptide chain. The parents of the neonate were heterozygous for the variant.

Discussion

ARPKD is one of the most common heritable disease in infancy and childhood, which attracts the early attention of clinicians.[4] Notwithstanding various types of ARPKD, the majority of patients are identified either in utero or at birth. The most severely affected fetuses have enlarged echogenic kidneys and oligohydramnios because of poor fetal renal output. The most significant result from oligohydramnios is pulmonary hypoplasia, so that the severely affected newborns do not have sufficient lung capacity to survive. Up to 30% to 50% of all patients die shortly after birth from respiratory insufficiency, while renal failure is rarely a cause of neonatal death. Our case died soon after birth due to progressive respiratory failure caused by pulmonary hypoplasia and severe respiratory distress. The previous fetus had been diagnosed with oligohydramnios by ultrasound in utero at 27-week gestation, indicating another affected child in the family.

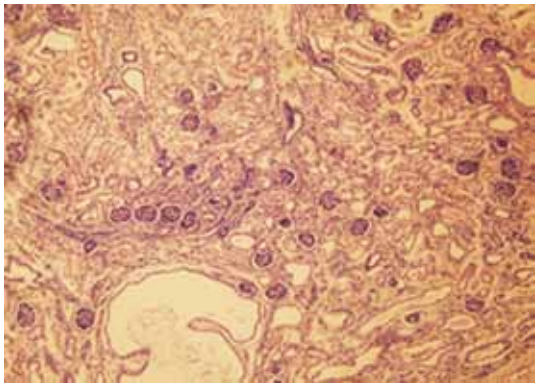

Fig. 1. Renal histology reveals multiple subcapsular cystic lesions (hematoxylin and eosin staining, original magnification × 20).

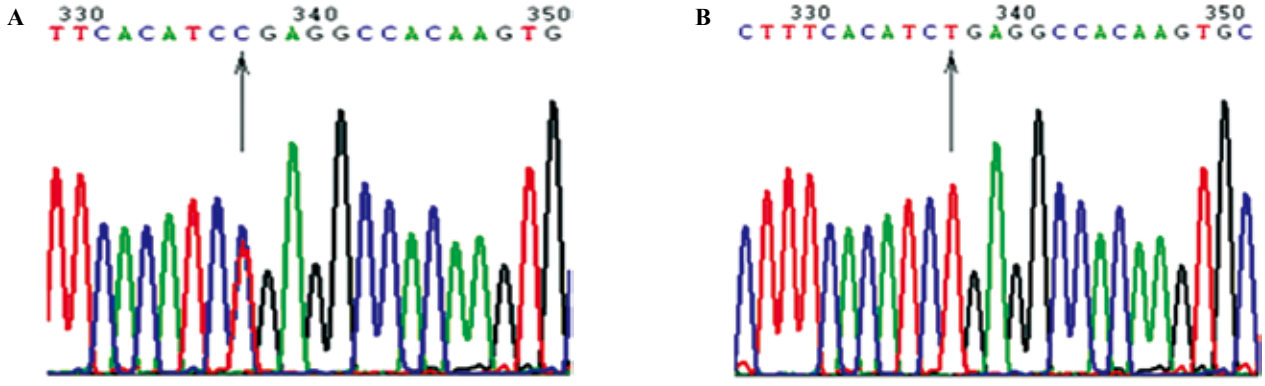

Fig. 2. Double-strand sequencing of *PKHD1*. **A:** heterozygous *PKHD1* mutation c.9319C>T (p.R3107X) in the mother; **B:** homozygous *PKHD1* mutation c.9319C>T (p.R3107X) in the neonate.

Case report

The clinical spectrum is much more variable than generally presumed. Most ARPDK cases manifest peri/neonatally with a high mortality rate during the first month of life, while presentation of ARPKD at later ages and survival into adulthood has been observed in a substantial number of cases. Bergmann et al[5] examined the clinical course of 164 neonatal survivors. In their report, patients who survived the first month of life, 95% were alive at 1 year, 94% at 5 years, and 92% at 10 years. For surviving patients, a wide range of associated morbidities can develop, including systemic hypertension, renal failure, portal hypertension, and renal and hepatic fibrosis. Despite intense active research, there is currently no disease-specific therapy for ARPKD. Clinicians can improve symptoms and prolong life through treatment of hypertension, anticipation and monitoring of extrarenal complications, and utilization of end-stage renal disease therapy.

Prenatal ultrasound findings of the enlarged kidneys, oligohydramnios, and absence of urine in the bladder suggest the diagnosis of ARPKD, but they are not diagnostic.[6] In all cases of congenital anomalies of the kidney with lethal ending, it is necessary to perform autopsy and genetic investigation. Characteristically seen in our study, the kidneys are enlarged but retain their reniform appearance, and the collecting tubules and the marked dilatation of the collecting ducts make the kidneys look spongy. Consistent with the previous observation that the severity of renal disease is proportional to the percentage of nephrons affected by cyst, the reported neonate had over 90% of the renal tissue filled with cysts and died within the 1st week of life. Liver involvement is always present in ARPKD patients and may be the predominant clinical feature. Even in the newborn with ARPKD, the liver demonstrates microscopic abnormalities. Liver lesion in our neonate is portal fibrosis surrounding an increased number of hyperplastic, ectatic biliary ducts with normal hepatocellular histology. The relative degrees of kidney and liver involvement tend to be inverse; children with severe renal disease usually have milder hepatic disease, and those with severe hepatic disease tend to evidence mild renal impairment.

PKHD1 mutation screening is a powerful diagnostic tool in patients suspected with ARPKD. *PKHD1* is an exceptionally large gene (470 kb) with a longest open reading frame transcript of 67 exons predicted to encode a 4074-amino acid (aa) (447 kDa). Thus, a total of 713 different *PKHD1* mutations are included in the locus-specific database (www.humgen.rwth-aachen.de). About one third of mutations are unique to a single family, and a small number are enriched in specific geographic areas. The most common mutation, c.107C>T (T36M), accounts for approximately 15% to 20% of mutated alleles, and has been found in a multitude of pedigrees of various ethnic origins. There are conflicting data on whether it is an ancestral change or occurs due to a frequent mutational event. A clear genotype/phenotype correlation has been described in ARPKD that missense changes are more frequently observed in patients with a milder clinical course, while chain-terminating mutations are more commonly associated with a severe phenotype.[7] In our neonate, we identified a nonsense mutation c.9319C>T (p.R3107X). The homozygous mutation carrier with c.9319C>T reported by Bergmann[8] had an induced abortion at 24-week fetal age because of oligohydramnios and enlarged kidneys. Autopsy revealed typical renal and hepatic pathological presentations of ARPKD.

Because of the significant morbidity and mortality of ARPKD, many parents of ARPKD children, especially who lost a child with severe symptoms, seek prenatal diagnosis to guide future family planning. Sonographic features of ARPKD may be noted early at the gestation of 24 weeks, but usually are not apparent until after the 30-week gestation.[9] *PKHD1* mutations characterized by direct sequencing is the only option for accurate genetic counseling and early prenatal diagnosis.[10]

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Ethical approval: This study was approved by the local ethical committee of the First Affiliated Hospital of Medical College of Xi'an Jiaotong University. Informed consent was obtained from the study participants.

Competing interest: No benefits in any form have been received from any commercial party related to the subject of this article.

Contributors: Zhou XH contributed to the conception and design of the study, interpretation of the results, and writing of the paper. All authors contributed to data collection and interpretation of the study.

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