

Diagnostic of Early Onset Polycystic Kidney Disease in Neonates

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ABSTRACT: Polycystic kidney disease represented by autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) have a major impact of mortality in children. We conducted a study of a premature infant with an estimated gestation date of 32 weeks with a presumptive prenatal diagnosis of right polycystic kidney. A 28-year-old primigravida with pre-eclampsia was admitted at the gynecology unit of Clinical Emergency County Hospital of Craiova. The clinical examination revealed a large abdominal distention due probably to the right polycystic kidney, suspected on prenatal ultrasound and radiography. The preterm neonate undergone right nephrectomy 5 days after birth. Histopathology of the kidney was performed in the Pathology Department of the Emergency County Hospital of Craiova and in the Center for Microscopic Morphology and Immunology of U.M.F. of Craiova. Microscopy revealed dilated cysts lined by simple cuboidal or flattened epithelium, and islets of remnant kidney parenchyma separated by edematous stroma. Immunohistochemistry for CD34 revealed incomplete blood arcades which did not seem to be in contact with all the tubular elements of the parenchyma, when compared to a control age-matched kidney. The patient had a favorable postoperative evolution, she was clinically stable on discharge from the hospital with a follow-up strategy including genetic testing.

KEYWORDS: ADPKD, polycystic kidney, premature, neonate, nephrectomy

Introduction

Polycystic kidney disease represented by autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) have a major impact of mortality in children.

In present, the incidence of autosomal dominant polycystic kidney disease is 1:400 to 1:1,000 and the incidence of ARPKD is 1:20,000 to 1:40,000.

A significant cause of renal failure in adults is proved to be ADPKD.

Actually a treatment of the cause does not exist.

There are specific therapies only for the complications of the disease. Both ADPKD and ARPKD are genetically transmitted diseases [1].

The clinical manifestations are consequences of the renal cysts formed in uterus [2,3].

These consist in high blood pressure, hematuria, proteinuria, lower back pain, renal lithiasis and altered renal function [3,4,5].

A severe neonatal onset can characterize ADPKD and ARPKD.

The difference is made by ADPKD which can have an insidious evolution until adulthood.

The cysts of the enlarged kidneys in autosomal dominant polycystic kidney disease can have unilateral or bilateral disposition detected by ultrasonography.

Both sexes are equally affected, but ADPKD, is more frequently diagnosed at birth than ARPKD.

The renal phenotype in males is more severely affected than females.

The mutations of the PKHD1 gene will determine a hepatorenal polycystic disease [6,7].

A "Potter-like" syndrome is characterized by pulmonary hypoplasia, bilateral nephromegaly, oligohydramnios and can determine a fetal dystocia with a difficult delivery.

Although neonatal intensive care has increased the newborns survival rate, the death percentage represents 25-30% of the polycystic kidney disease newborns as a consequence of their respiratory insufficiency [8,9].

According to the study of Roy S and Kaplan B.S, almost 50% of the affected newborns that

survive throughout the neonatal period, will develop renal insufficiency within the first decade of life.

The researchers have established the main causes of the morbidity as follows: nephromegaly along with the cysts of the renal collecting duct which determined high blood pressure and end stage renal disease, biliary dysgenesis which ended up as hepatic fibrosis.

As a consequence of their congenital hepatic fibrosis, the patients will be affected by esophageal varices, splenomegaly, portal hypertension and gastrointestinal hemorrhage [8,10].

Case presentation

We conducted a study of a premature infant born in October 2018 with an estimated gestation date of 32 weeks with a presumptive prenatal diagnosis of right polycystic kidney.

A 28-year-old primigravida with pre-eclampsia was admitted at the gynecology unit of Clinical Emergency County Hospital of Craiova.

She gave birth to a female infant by caesarean section.

According to the mother's last menstrual period, the pregnancy was dated at 32 weeks.

The newborn was scored according to the expanded New Ballard Score [11] for neuromuscular and physical parameters.

A score of 20 correlated with the mother's last menstruation date, had a result of apremature neonate.



Fig.1. Thoracoabdominal radiograph which shows a distended abdomen with a right flank mass and an elevated diaphragm caused by severe renal enlargement

The baby girl was born with an Apgar Score [12] of 8 at 1 minute and 5 at 5 minutes of birth.

At birth the preterm neonate had a spontaneous breathing and she was admitted to the neonatal intensive care unit.

The clinical examination revealed a large abdominal distention due probably to a right polycystic kidney suspected on a thoracoabdominal radiograph (Fig.1) and a prenatal ultrasound examination (Fig.2).

The patient was placed in an incubator and a parenteral nutrition was initiated.

A maternal vaginal infection with E. Coli (sensitive to ceftriaxone) was identified during labor.

In order to prevent a neonatal sepsis, a 7 days ceftriaxonetherapy with 50mg/kg/dose, 2 times a day was included in the neonate's therapy.

Aminophylline therapy was started to decrease the risk of apnoea.

The following vital parameters were monitored: ECG, respiration, blood oxygen saturation, body temperature.

Also the stool and urine output were recorded on a chart.

The blood pressure for her gestational age had normal values during her stay in the hospital.

48 hours after her birth the infant started to develop respiratory distress syndrome with tachypnoea (respiratory rate of 80/minute), xiphoid and lower chest retractions, marked nasal dilatation and noisy respiration in the form of a grunt.

The distress was associated with desaturation on pulse oximetry.

Intubation was made with a 3mm endotracheal tube and mechanical ventilation was initiated.

The infant was examined by a pediatric surgeon who decided that a nephrectomy is required taking into account the mass effect of the polycystic kidney.

The preterm neonate underwent right nephrectomy 5 days after her birth (Fig.2).

Macroscopically, the resected kidney parenchyma seemed to be massively replaced by thin walled cysts that could be visualized through the capsule, and contained a serous clear fluid (Fig.2).

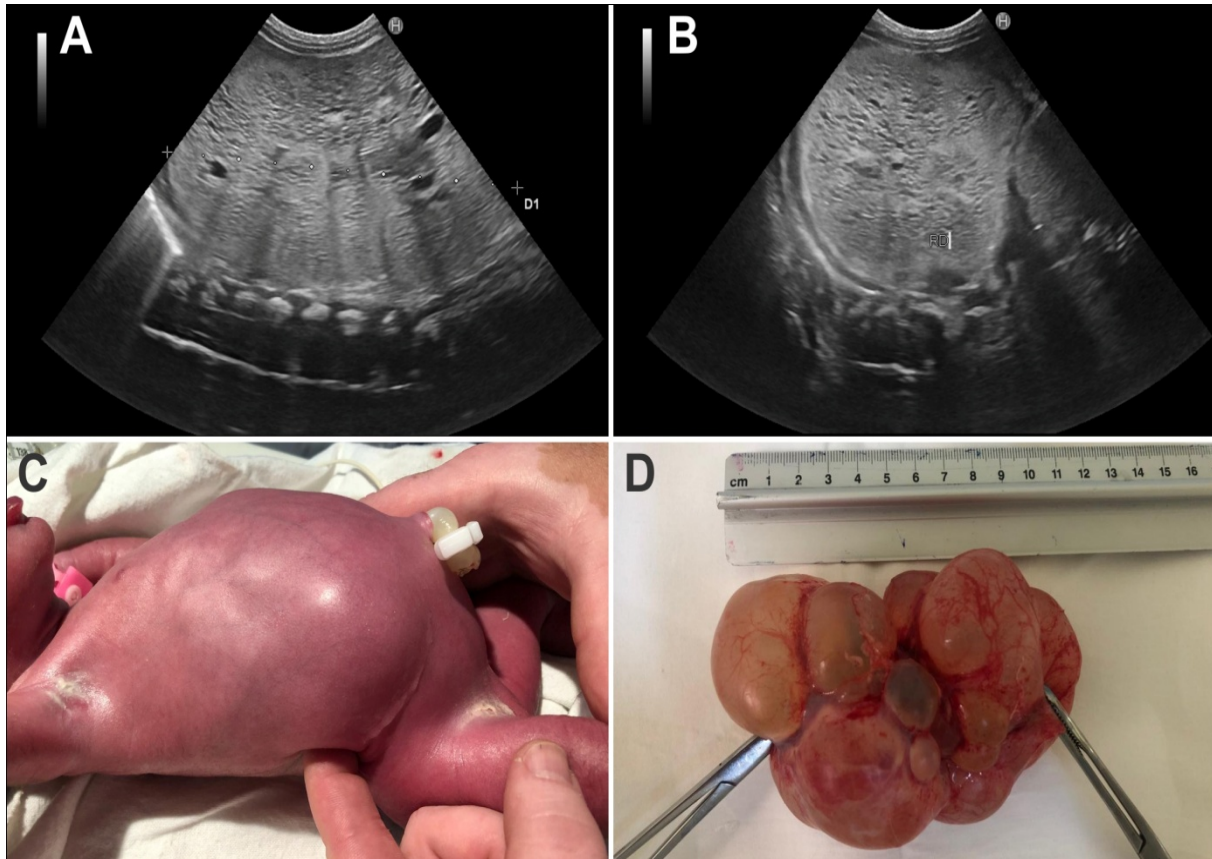


Fig.2. A,B-Neonatal renal ultrasound: enlarged hyperechogenic right kidney-11/6cm with the loss of corticomedullary differentiation, renal parenchyma replaced by multiple cysts. C-large abdominal distension due to the right polycystic kidney. D-Macroscopic view of the surgically removed kidney shows multiple large cysts filled with a serous clear fluid that had developed under the capsule

Histopathology of the kidney was performed in the Pathology Department of the Emergency County Hospital of Craiova, and in the Center for Microscopic Morphology and Immunology of U.M.F. of Craiova.

After fixation in 10% neutral buffered formalin, the kidney was processed for paraffin embedding, and sectioning, and immunohistochemistry was performed for the anti-CD34 (mouse, Dako, code M7165, 1:50), anti-CLA (mouse, Dako, code M0701, 1:100), and the anti-collagen IV (mouse, Dako, code M0785, 1:50) primary antibodies.

Briefly, after antigen retrieval and peroxidase blocking, the primary antibody was incubated on the sections overnight at 4C, and the next day a species-specific secondary linked with HRP was

added on the slides for 30 minutes (Nichirei Bioscience, Tokyo, Japan).

After washing, the enzyme was visualized with 3,3'-Diaminobenzidine tetrahydrochloride hydrate (DAB) (Dako, Glostrup, Denmark), and the slides were coverslipped with a xylene-based medium (DPX, Sigma-Aldrich, St. Louis, MO, USA).

Microscopy revealed dilated cysts lined by simple cuboidal or flattened epithelium, and islets of remnant kidney parenchyma separated by edematous stroma (Fig.3).

Both proximal and distal tubules were occasionally distended, and sometimes dilated Bowman's spaces could be noted in the glomerulus.

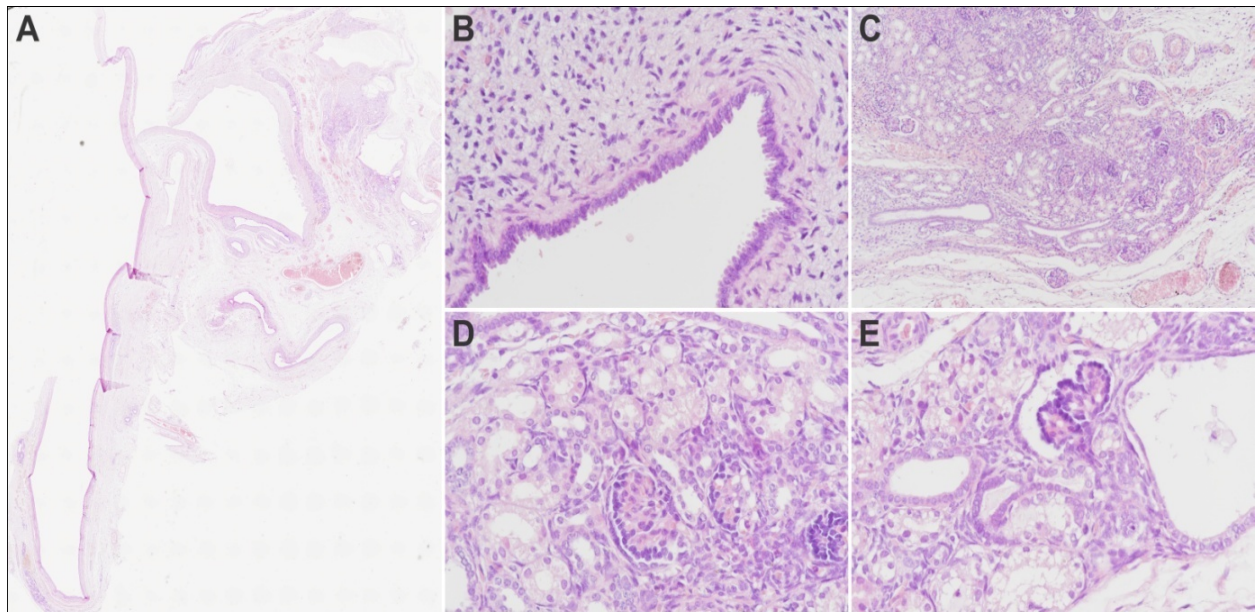


Fig.3. Histopathology reveals many cysts lined by a cuboidal-flat epithelium (A,B), with remnant kidney parenchyma in between the cists (C-E). Sometimes dilated tubules or Bowman's spaces can be identified (E). Hematoxylin-eosin staining, A-5x scan, B-, D-E-40x, C-10x

Immunohistochemistry for CD34 revealed incomplete blood arcades which did not seem to be in contact with all the tubular elements of the

parenchyma, when compared to a control age-matched kidney (Fig.4).

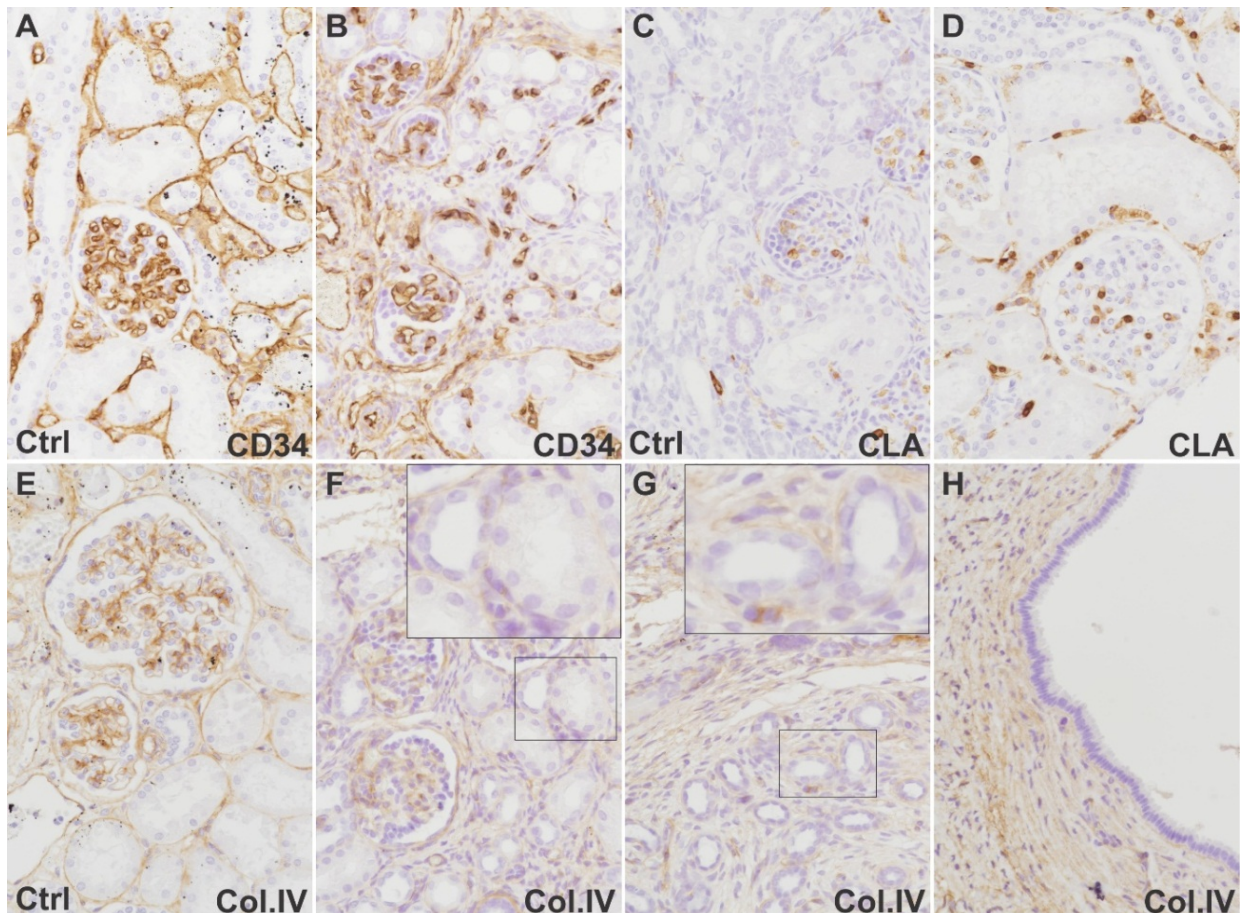


Fig.4 Immunohistochemistry for CD34 shows incomplete blood vessel arcades (B vs A), increased inflammation as visualized by an anti-CLA antibody (D vs C), and discontinuous basement membranes in some of the tubes (E-G) or the cyst walls, based on the anti-collagen IV antibody (H), 40x

Based on anti-CLA immunohistochemistry, it was next clear that there were much more inflammatory cells within the remnant parenchyma compared with the control.

When we evaluated the basement membranes (based on anti-collagen IV immunohistochemistry), it was very interesting that we found discontinuous basement membranes surrounding the proximal and distal tubules, but continuous around blood vessels and the vascular glomerulus.

This discontinuous pattern was also present under the epithelium lining the cysts, and altogether these data seemed to be showing that this parenchyma was not functional, or at least it did not exhibit a clear cut sub-epithelial barrier of collagenous basement membranes and fully functional capillaries.

Second post-operative day the feeding process with breast milk was initiated via nasogastric tube.

The feeds were progressively increased so that the aspirates were minimal.

Nevertheless, the infant was on full oral feeds by day 18 of life.

She was extubated 16 days after her birth.

The patient had a favorable postoperative evolution, she was clinically stable on discharge from the hospital with a follow-up strategy including genetic testing.

During her stay in the hospital, the patient undergone 1 platelet transfusion for thrombocytopenia at 13 days after her birth (platelet count=30. 510/mmc) and two red blood cell transfusion 15 days after her birth (Hemoglobin=10.08g/dl, Hematocrit=31,8%) and 31 days after her birth (Hemoglobin=11.5%, Hematocrit=30.7%).

The blood pressure values were normal and the diuresis values were of 3-4ml/kg.

The positive neonatal ultrasonography results were correlated with the abdominal radiograph and also with the positive family history of polycystic kidneys (maternal grandmother).

Discussion

Preterm birth rates are rising globally, and it actually represents one of the biggest risk factors for neonatal morbidity and mortality.

Multiple complications are associated with preterm birth.

Techniques in the management of preterm birth in the developed world have undergone significant advances, with outcomes for neonates born prematurely improving greatly over the past few decades.

In 2005, the WHO estimated that globally 9.6% of births are preterm.

Preterm infants are disproportionately over-represented in neonatal mortality rates with estimates showing that a quarter of perinatal deaths are attributable to complications of prematurity.

There are a number of pharmacological approaches which have shown demonstrable improvement in neonatal outcomes.

The incidence of the respiratory distress syndrome along with the necrotizing enterocolitis have been strongly reduced since the use of antenatal steroids.

Even incomplete courses of antenatal steroids have been shown to give some benefits to extremely premature infants.

The importance of antenatal steroids cannot be overstated.

They are generally widely available, easy to administer, even in the community, and have minimal risk of adverse effects to mother and baby.

A recent study estimated that 500000 neonatal lives could be saved annually if antenatal steroids were given appropriately to all mothers going into preterm labor [13].

Regarding our study, as soon as the mother was admitted in the gynecology ward and diagnosed with severe preeclampsia, she has undergone a caesarean section, so the antenatal steroids therapy was not done.

Moreover, the newborn had multiple risk factors to develop respiratory distress syndrome as being born as a preterm with a pathology of enlarged polycystic kidney that can limit the diaphragmatic excursions.

Another pharmacological agent used to attempt to counteract some of the problems of prematurity is aminophylline [13].

Apnea is typical for preterm neonates.

In order to reduce the episodes of hypoxemia and bradycardia, numerous studies showed the positive effect of the methylxanthines (caffeine, aminophylline).

There were made five trials of 192 neonates with recurrent apnea registered in the Oxford Database Perinatal studies from 1966 to 2010.

The results showed the efficacy of using methylxanthines along with IPPV by reducing the apneic episodes in the first seven days of use.

Regarding the long term effects, caffeine should represent the first option therapy to aminophylline [14].

Caffeine is generally the preferred option in our neonatal unit for its lower toxicity.

However, the newborn has received aminophylline because at that period of time, caffeine was not available from the pharmacy.

The long-term risk of neurodevelopmental disability associated with aminophylline administration needs to be taken into account [15].

Use of prophylactic antibiotics is controversial but evidence suggests that prophylactic antibiotics can reduce incidence of necrotizing enterocolitis in preterm infants, however the issue is fraught with difficulty with challenges of antibiotic resistance and antibiotic side effects [13].

Recent studies proved that maternal vaginal infection with *Escherichia Coli* can determine intra-amniotic infection and neonatal sepsis.

Genital tract *E Coli* infections of pregnant women were more aggressive than non-pregnant ones.

The neonatal sepsis may be caused by existence of hemolysis and cytotoxic necrotizing factor during pregnancy. [16].

During labor, a maternal vaginal infection with *E. Coli* (sensitive to ceftriaxone) was identified.

In order to prevent a neonatal sepsis, the newborn has received a ceftriaxone therapy.

A new research established that *E Coli* collected from infected intraamniotic liquid had ampicillin and gentamicin resistance.

In conclusion, the first line treatment based on cephalosporins for mothers and newborns had good results in peripartum sepsis [17].

Moreover, right enlarged polycystic kidney was an important factor in our patient respiratory distress syndrome.

The right nephromegaly had a mass effect pressing the stomach and the intestines to the left flank.

Her left kidney was not polycystic, it had normal dimensions for her gestational age and it was functional so it was no need for a dialysis.

The neonate had a good outcome after the surgical procedure.

The numerous reports of neonates with ADPKD sustain that unilateral or bilateral nephrectomy has improved ventilation and nutrition.

However, it was not decided an optimal approach regarding this pathology.

Taking into account the high surgical risks of the neonates with severe respiratory distress it

was not clearly stated the positive respiratory outcome.

There were reported positive outcomes regarding the respiratory support for neonates with unilateral or bilateral nephromegaly for both cases: the newborns who underwent nephrectomy and the ones who were not operated.

The decision of nephrectomy for neonates with ADPKD must be highly individualized because of the early dialysis consequences [18].

Around the 15th week of gestational age, a prenatal diagnosis of polycystic kidneys can be suspected based on hyperechogenic enlarged kidneys.

Our patient had a presumptive prenatal diagnosis of polycystic kidneys.

The polycystic kidney disease can have recessive pattern (ARPKD-autosomal recessive polycystic kidney disease) or an autosomal dominant pattern (ADPKD-autosomal dominant polycystic kidney disease).

Literature states that that ADPKD is more common in female patients, and ARPKD in male patients [19,20].

The anamnestic data present obtained from the patient record sustain the maternal inheritance pattern of ADPKD.

A diagram presented in the Third Edition of the Clinical Pediatric Nephrology [21] shows that both ADPKD and ARPKD have a positive family history of polycystic kidney disease, but only in ADPKD the disease is unilateral.

The ARPKD has a bilateral polycystic pathology of the kidneys.

Also, the renal parenchyma in ADPKD is replaced by multiple large cysts and the kidney loses his normal shape, whereas in ARPKD there are multiple cysts of small dimensions that do not modify the renal shape.

All these characteristics are specific for an autosomal dominant polycystic kidney for our case.

Conflicts of interest

None to declare.

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