Reminder of important clinical lesson

Autosomal recessive polycystic kidney disease: the importance of autopsy of suspected cases and genetic counselling

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Summary

Autosomal recessive polycystic kidney disease (ARPKD) is a common inheritable cystic renal disease that has a profound effect on the growing fetus and on subsequent pregnancies, being fatal in 30% to 50% cases in the neonatal period. Prenatal imaging studies are only suggestive of the disorder and it is evident only from the second trimester onwards. Prenatal molecular linkage analysis can identify the disorder, but have a prerequisite of previous DNA analysis of parents and one sibling. ARPKD can be accurately diagnosed on characteristic histopathological features if an autopsy is performed in cases of infant death where the prenatal imaging studies and clinical findings are suggestive of the disease. A case of the characteristic histopathological findings of ARPKD on autopsy of a live-born neonate who died shortly after birth, with prenatal ultrasonographic findings suggestive of renal cystic disease, is presented.

BACKGROUND

Autosomal recessive polycystic kidney disease (ARPKD) is a common heritable cystic renal disease with an estimated incidence of 1 in 6000 to 50 000 live births.^{1 2} The disease results in cystically enlarged kidneys and development failure of the biliary collection system. Respiratory insufficiency subsequent to oligohydramnios has been reported to be the cause of death during or shortly after birth in 30% of the affected neonates.³ Ultrasonography findings suggestive of the disease are evident only after the second trimester and as such it can be serially used as a screening modality after 15 weeks.⁴ Confirmation of the diagnosis is based on histopathological examination, which must be performed in cases of neonatal death where prenatal imaging studies and history are suggestive of ARPKD.

CASE PRESENTATION

Autopsy findings performed on a live-born neonate girl, who died 5 h after birth with significant pathological findings, were as follows.

Kidneys

Grossly, bilaterally enlarged kidneys spongy in consistency were seen (right: 7 cm × 4 cm and 85 g, left: 8 cm × 4.5 cm and 105 g), and the outer surface was greyish with areas of congestion, with multiple small cysts (less than 5 mm) with intact renal capsule. The cut surface showed multiple small cysts, present throughout the renal parenchyma, which were filled with clear white fluid (figure 1A). Microscopic examination revealed that these cysts were dilated ducts forming oval sac-like structures lined by cuboidal epithelium, filled with eosinophilic hyaline material and involving the cortex and medulla, with normal nephrogenesis (figure 1B–D).

Liver

Grossly, the liver was enlarged, weighing 190 g, and on the cut surface showed multiple small cysts in hepatic parenchyma (largest measuring 0.8 cm) filled with a yellow-coloured fluid (figure 2A). On microscopic examination enlarged portal areas forming interconnecting sacs with proliferating angulated bile ducts along with periportal fibrosis and congestion were seen (figure 2 B–D).

Lungs

Grossly, both lungs were hypoplastic. Microscopic examination showed atelectasis with thickened alveolar septa with debris, macrophages and denudation of alveolar epithelium. There was no history of any drug intake by the mother except for iron and folic acid supplements. Her medical history revealed the neonatal death of a live-born girl with abdominal distension 2 years previously due to respiratory distress 3 days after birth. This pregnancy was not medically supervised with any available records.

INVESTIGATIONS

Ultrasonographic evaluation was performed on the 18th, 29th and 35th weeks. Initial ultrasonographic investigations showed a normal fetus with no detectable congenital abnormality and sufficient amniotic fluid. A second examination revealed an amniotic fluid index of 6 cm with no congenital abnormality. The last examination detected severe oligohydramnios with large bulky fetal kidneys and a small thoracic cavity with possibility of lung hypoplasia, along with fetoplacental and mild uteroplacental insufficiency.

DIFFERENTIAL DIAGNOSIS

Prenatal ultrasonographic findings of renal cystic changes can be due to glomerulocystic kidney disease, multicystic

Figure 1 Gross and microscopic kidney findings. A. Grossly enlarged kidney, with cut surface showing microcystic spaces. B. Dilated ducts forming round to oval sacs with normal nephrogenesis (H&E $\times 40$). C. Dilated ducts with normal nephrogenesis showing cuboidal epithelium (H&E $\times 100$). D. Dilated tubules with inspissated eosinophilic material (H&E $\times 400$).

Figure 2 Gross and microscopic liver findings. A. Grossly enlarged liver with cut surface showing areas of congestion and cysts. B. Enlarged portal areas with proliferating angulated bile ducts, periportal fibrosis and congestion (H&E $\times 40$). C. Interconnecting sacs resulting from abnormal biliary differentiation (H&E $\times 100$). D. Periportal fibrosis with abnormal bile duct differentiation (H&E $\times 400$).

renal dysplasia, cystic renal dysplasia, hydronephrosis or vesicoureteral reflux, and identification of the exact cause can be difficult, especially during early pregnancy. However, characteristic gross and microscopic findings on histopathological examination of the affected organ(s) can accurately identify the cause of renal cysts and make a confirmatory diagnosis.

OUTCOME AND FOLLOW-UP

The neonate was diagnosed as having ARPKD. Her parents were advised to undertake chromosomal analysis and genetic counselling before planning another pregnancy.

DISCUSSION

ARPKD is a common heritable cystic renal disease with an estimated incidence of 1 in 6000 to 50 000 live births.^{1 2} The diagnosis of ARPKD is based on characteristic histopathological findings of the kidney and liver; the kidneys are grossly enlarged with multiple cysts on the external surface that involve the cortex and medulla and are located in collecting ducts and tubules, lined by cuboidal epithelium; grossly, cysts are also present in an enlarged liver where they form due to enlarged portal areas forming anastomosing channels, with the biliary structures forming dilated sacs.⁵ Hepatic fibrosis is an essential diagnostic criterion for this autosomal recessive disease.⁶ The involvement of the renal collecting system and hepatic ductal plate malformation is due to failure of terminal differentiation of the collecting duct and biliary systems, causing oligohydramnios leading to pulmonary hypoplasia which is the cause of morbidity, in 30% of cases.^{3 7} Similar histopathological findings were evident on autopsy in our case.

Prenatal diagnosis using fetal sonography can be unreliable, especially in early pregnancy; however, serial ultrasound evaluation for hyperechogenicity resulting from presence of multiple microcysts, dysplasia or tubular dilatation starting at 15 weeks can be used, as a screening modality.⁴ Serial ultrasonographic evaluation in this pregnancy showed decreasing amniotic fluid level and enlargement of kidneys as the pregnancy progressed.

The genetic abnormality linked to ARPKD is limited to chromosome 6p21.1-p12, is a single gene disorder (PKHD1 gene) and is due to protein polyductin also known as fibrocystin.⁸ Haplotype based prenatal testing in pregnancies 'at risk' for ARPKD has been proposed, albeit with absolute prerequisite of confirmed diagnosis of the disorder in previously affected sibling(s).²

We conclude that an autopsy with histopathological examination must be performed in cases of infant death for

a confirmatory diagnosis of ARPKD where prenatal ultrasonographic findings and clinical history are suggestive of the disease.

Learning points

- ▶ The diagnosis of autosomal recessive polycystic kidney disease (ARPKD) is based on characteristic histopathological findings of kidneys and liver.
- ▶ Serial ultrasonographic examinations are a useful prenatal screening modality for ARPKD.
- ▶ In cases of first pregnancy associated with neonatal death where antenatal ultrasonographic findings are suggestive of ARPKD, an autopsy with emphasis on histopathological examination of the kidneys and liver must be performed to confirm or negate ARPKD.
- ▶ Chromosomal analysis of the parents and evaluation for polyductin/fibrocystin protein in affected fetuses are important diagnostic tools.
- ▶ To prevent future loss of pregnancy, the parents should be given genetic counselling in all such cases.

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Competing interests None.

Patient consent Obtained.

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