Nephrectomy in an autosomal recessive polycystic kidney disease (ARPKD) patient with rapid kidney enlargement and increased expression of EGFR

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Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is a hereditary disorder with an incidence of 1/10 000 to 1/40 000 individuals [1,2]. ARPKD is caused by mutations in the PKHD1 gene on chromosome 6p12 [3,4]. Prenatally, oligohydramnion, enlarged kidneys and lung hypoplasia with the typical Potter facies become evident. Principal histological manifestations involve the fusiform dilation of renal collecting ducts and distal tubuli as well as dysgenesis of the hepatic portal triad (so-called ductal plate malformation with congenital hepatic fibrosis and hyperplastic biliary ducts). The spectrum of the disease is highly variable ranging from severe perinatal manifestations to later onset and milder forms. Severe phenotypes are more often associated with truncating PKHD1 changes than moderately affected individuals [5,6]. Especially children with severe renal disease show a high perinatal mortality. Death is often caused by respiratory insufficiency due to lung hypoplasia and displacement of the diaphragm by bilateral renomegaly. The reported incidence of severe respiratory problems, including pneumothoraces and respiratory insufficiency, is up to 75% in patients presenting early with renal failure [7,8] and most of the children with lung hypoplasia die from respiratory insufficiency shortly after birth. Among the neonatal survivors, 30% show fast progression to renal insufficiency [2,8–11]. Another common problem in children with ARPKD, especially at onset, is arterial hypertension with a prevalence of 55–100% [8,9,11]. Volume overload due to poor renal function and hyponatraemia with resultant hyperreninaemia were suggested to be causal factors [10,12]. Up to 83% of patients develop congenital hepatic fibrosis, often with portal hypertension without alteration of liver synthesis and only mild alterations of serum transaminase levels [7,8,11,12]. First-year survival rates in patients with ARPKD vary from 19% [7] to over 90% [2,11]. Causes of early death are sepsis or respiratory failure. Especially children with high kidney volumes and poor renal function develop severe respiratory problems or nutritional problems. One therapeutic option may be unilateral or bilateral nephrectomy but only few cases are reported in whom uni- or bilateral nephrectomy led to respiratory improvement, better enteral nutrition and more effective peritoneal dialysis [13,14]. Many of the patients who survived the first year of life successfully underwent renal transplantation [13,14].

We report the case of an infant diagnosed for ARPKD which showed an unusual massive growth of kidney volume within 10 days. Unilateral nephrectomy was performed as rescue therapy and haemodialysis was performed for several days without major technical complications. Our patient died 27 days after birth due to complications derived from pulmonary hypertension.

Case report

A female newborn of non-consanguineous parents with an gestational age of 36 + 0 weeks (birth weight 2480 g, length 43 cm and head circumference 32 cm) was referred to our clinic on the second day after delivery because of arterial hypertension, increasing episodes of apnoea and kidney failure. Prenatally, accelerated kidney growth (Figure 1) and oligohydramnion was observed requiring four refills of amniotic fluid and the diagnosis of ARPKD was assumed. Ultrasound showed a typical pepper–salt pattern for ARPKD with small medullary cysts not exceeding 0.6 cm each (Figure 2A). MRI of the abdomen was not feasible in this critically ill patient. Chest x-ray showed typical...
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Fig. 1. Growth percentiles showing the rapid prenatal and postnatal development of the kidney length in our patient (dashed line) compared to the average kidney length (solid line). The table shows the increase of the right and left kidney volume prenatal and postnatal.

patterns of lung hypoplasia. The diagnosis of ARPKD could later be confirmed histologically and genetically. In total, three PKHD1 mutations were identified: c.107C>T (p.Thr36Met) in exon 3, c.2414C>T (p.Pro805Leu) in exon 24 and c.9530T>C (p.Ile3177Thr) in exon 58. Abdominal ultrasounds of the parents were normal and the family history was reported to be unremarkable. The proposita has two elder healthy siblings.

Within the first 10 days of life, kidney volume increased from 100 ml to 325 ml per kidney followed by respiratory insufficiency (Figure 1, Figure 2B). Mechanical ventilation became necessary on the fourth day of life caused by dislocation of the diaphragms due to voluminous kidneys, mild lung hypoplasia and increasing oedema resulting from renal insufficiency with oliguria. Treatment with furosemide and hydrochlorothiazide was started on the second day of life resulting in a maximum diuresis of 35 ml/kg/day. Because of arterial hypertension with systolic blood pressure values up to 122 mmHg (mean arterial pressure [MAP] 93 mmHg; >95th percentile), amlodipine and diuretics were used as antihypertensive treatment but normalization of blood pressure could not be achieved. High ventilation pressure (inspiratory pressure >30 cmH2O) and increasing kidney volumes with renal failure led to the decision to remove the left kidney as rescue therapy at Day 14. During surgery, a Shaldon catheter was implanted in the right subclavian vein and renal replacement therapy via continuous veno-venous haemodialysis (CVVHD, dialyzer BLS803, Baxter, Deerfield, IL, USA) was performed using heparin as anticoagu-

lants. Maximum arterial bloodflow was 24 ml/min. Ultrafiltration rate of 45 ml/h was achieved; dialysis was performed over 11 days without major complications. However, liver failure and thrombocytopenia due to bone marrow failure resulted in diffuse bleeding. Ventilation problems, including development of pulmonary hypertension with echocardiography showing moderate tricuspid insufficiency with a pressure gradient >100 mmHg and right-ventricular hypertrophy, became more obvious within the following days. This prompted high frequency oscillation (HFO) and use of nitric oxide. Our patient died 27 days after birth following complications derived from pulmonary hypertension and multiple organ failure.

Discussion

ARPKD is a rare diagnosis which might cause end-stage renal disease (ESRD). We recently reported that ~60% of ARPKD patients undergo dialysis treatment up to an age of 20 years [11]; however, only 14% of ARPKD patients develop ESRD within the first 5 years of life [11]. Newborns with perinatally diagnosed massive enlargement of the kidneys have a poor prognosis and normally die of respiratory problems within the first days of life while most of the neonates without pulmonary hypoplasia survive. Infants with slow progression to ESRD who survive the first
months have a 50 to 80% chance to mature to adult age [1]; some of these patients were first diagnosed as adolescents or young adults. In this respect, only few studies of the long-term morbidity associated with ARPKD exist [11,15]. Our case is different from other reported cases since our patient showed an even more progressive enlargement of the kidneys within few days (Figure 1).

Unilateral nephrectomy for infants with severe perinatal ARPKD has been described as rescue therapy in three cases so far [16,17]. Although the number of reported cases is small, bilateral nephrectomy with subsequent peritoneal dialysis is the favoured method in most centres [13,18–20]. All patients presented enlargement of both kidneys and respiratory problems over months. Unilateral nephrectomy was performed on the 14th day of life as rescue therapy assuming an abdominal compartment syndrome as a possible cause of renal failure. In contrast, peritoneal dialysis was never an option in our patient due to the unusually rapid progression of kidney growth with thinning of peritoneum and subsequent difficulties in closing the peritoneal cavity. Therefore CVVHD was performed after nephrectomy, the dialysis treatment was effective and no technical problems occurred. Earliest renal replacement therapy by renal transplantation after bilateral nephrectomy was reported in two infants at the age of 9–15 months [13,19] but is not an option in newborns.

The exigent question in the reported case aims at the reason for the unusually fast enlargement of the kidneys and which growth stimuli might have been involved. One may speculate that the PKHD1 mutational load of our patient is in line with the severe clinical outcome. Our patients were shown to carry three missense mutations of the PKHD1 gene. The c.107C > T (p.Thr36Met) mutation, which is by far the most frequent PKHD1 mutation, has been recently categorized as a rather severe change [11]. Although mutation analysis of the parents of our patient was not possible, extensive data compiled in the PKHD1 mutation database (http://www.humgen.rwth- aachen.de) strongly suggest that the two mutations, c.2414C > T (p.Pro805Leu) and c.9530T > C (p.Ile3177Thr), occurred tandemly in cis on the same parental allele. Most patients harbouring the specific c.2414C > T (p.Pro805Leu)/c.9530T > C (p.Ile3177Thr) allele died perinatally, independent of the mutation on the other parental chromosome [5], allowing the careful categorization as a rather severe change, too. As ARPKD patients have been described so far carrying c.9530T > C (p.Ile3177Thr) alone, clarification of the consequences of the non-conservative, evolutionarily highly conserved missense change c.2414C > T (p.Pro805Leu) awaits identification of a patient bearing this specific mutation on one or both disease alleles alone. Rossetti et al. [21] reported a patient who carried the same combination of missense mutations as our patient showing a similar clinical course with oligohydramnion, enlarged kidneys and perinatal death. Overall, the severe clinical development of our patient may well be explained by the combination of these three missense mutations of the PKHD1 gene. Nevertheless, it is widely recognized and further corroborated by intrafamilial clinical variability among affected siblings in ARPKD [11] that resulting phenotypes frequently cannot be simply explained on the basis of the PKHD1 genotype but probably may also depend on the background of other genes, epigenetic factors and environmental influences. It is tempting to speculate that modifier genes that have been shown to influence the disease severity in mouse models for polycystic kidney disease may also modulate the phenotype of human ARPKD [22,23].

Given the massive and rapid kidney growth, we speculated that proteins like the epidermal growth factor receptor (EGFR) and associated signalling targets are abnormally expressed in the cystic renal epithelia of our patient. Increased expression of EGFR has been demonstrated to promote epithelial hyperplasia by binding EGF/TGF-α which generates mitogenic signals [24,25]. This may lead to progressive enlargement of cysts in both murine and human ARPKD [24,25]. Richards et al. [26] demonstrated that a mutation leading to diminished EGFR tyrosine kinase activity decreases cyst formation significantly in mice. All these findings favour a crucial role of EGFR in cyst formation. In our patient, we also demonstrated an increased expression of EGFR (Figure 3) as well as an up-regulation of several components (S6-kinase and 4E-binding protein 1) of the mTOR signalling pathway (data not shown), the latter has been shown to be crucial for the regulation of cell growth. The abnormal expression of different cell growth markers might explain the extremely high level of...
proliferation of the cystic epithelia in our patient leading to her severe phenotype.

Besides the genetically programmed disadvantages, our patient died of severe pulmonary hypertension. In the literature, endothelial dysfunction and hypercontraction of vascular smooth muscle cells are discussed as possible causes of pulmonary hypertension and improvement of this condition may be achieved by NO ventilation. Our patient did not improve under NO ventilation. This might be due to lung hypoplasia after oligohydramnion and possibly aggravated by thrombosis of alveolar capillaries after recurrent substitution of coagulation factors (fresh frozen plasma). Another reason could be dysplasia of alveolar capillaries, which is described as a major cause of pulmonary hypertension unresponsive to NO ventilation and other supportive therapy in the first days of life. This disorder is a rare entity often associated with congenital malformations including renal and urological anomalies [27]. The parents declined autopsy; therefore, we could not prove our speculations.

In conclusion, we report a case of ARPKD in a newborn with unusually rapid progression of the renal growth. The rapid kidney enlargement might be explained by the PKHD1 genotype and overexpression of EGFR. Uni- or bilateral nephrectomy should be considered to be performed early with consecutive renal replacement therapy. Haemodialysis seems to be an option when peritoneal dialysis is impossible to perform.

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References


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