Rare disease

A complex case of congenital cystic renal disease

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Summary

This case outlines the potential complexity of autosomal recessive polycystic kidney disease (ARPKD). It highlights the challenges involved in managing this condition, some of the complications faced and areas of uncertainty in the decision making process. With a paucity of published paediatric cases on this subject, this should add to the pool of information currently available.

BACKGROUND

Autosomal recessive polycystic kidney disease (ARPKD) is a condition affecting 1 in 20 000 of the population.¹ It is associated with a variety of mutations on the PKHD1 gene on the short arm of chromosome 6 which codes for fibrocystin.²

This is a growth factor receptor-like protein, associated with the primary cilia, which appears to play a role in regulating proliferation and differentiation of renal and biliary epithelial cells. Malfunction of this may therefore be involved in the progressive cystic dilatation of the renal collecting ducts and dysgenesis of the bile duct plate that occurs in ARPKD and related conditions.³ The phenotype can be diverse with varying degrees of associated morbidity and mortality. Blyth and Ockenden have categorised ARPKD into perinatal, neonatal, infantile and juvenile forms according to the age at presentation, associated clinical symptoms and pathology.⁴ In the perinatal and neonatal forms, presentation is early with significant kidney enlargement, oligohydramnios, pulmonary hypoplasia and Potters's Facies. In the latter groups, renal involvement is less significant and there are more complications as a result of congenital hepatic fibrosis.

The main principles of management are to control hypertension, monitor and support deteriorating renal function and monitor and manage portal hypertension.

This is a complex process that requires careful and considered multi-disciplinary medical and surgical input. The understanding and management of this condition continues to evolve. Relatively few paediatric cases have been published in the literature. The difficulties and complications encountered in this case, which were ultimately overcome to give a good outcome, will add to the pool of information currently available and help inform others managing patients with this challenging condition.

CASE PRESENTATION

This patient was born at 38 weeks gestation by spontaneous vertex delivery after an uncomplicated pregnancy. Birth weight was 6lb 6oz.

She required initial resuscitation with positive pressure ventilation but continued to have increased respiratory effort with grunting. She was taken directly to the special care baby unit (SCBU). A chest x-ray demonstrated a sizeable right-sided pneumothorax requiring insertion of a chest drain. She required in total 3 days of ventilation and remained in SCBU for 2 weeks. During this time she was noted to have bilateral abdominal masses. Ultrasound showed this to be due to massive cystic enlargement of both kidneys (figure 1). The liver was also noted to be enlarged and cystic. Initial serum biochemistry revealed a urea of 4.9 mmol/l with creatinine marginally elevated at 79 µmol/l. Liver function tests were normal.

On the basis of these clinical and radiological findings, a diagnosis of ARPKD was made by the renal physician.

There was no family history of renal disease and no consanguinity.

The subsequent treatment and management of this case are described below.

INVESTIGATIONS

- ▶ Diagnosis in this case
- ▶ Based on US findings as shown in figure 1. The kidneys were enlarged to 10 cm of length and remained consistently enlarged at approximately this size on serial scanning with the presence of cystic changes.

DIFFERENTIAL DIAGNOSIS

Types of cystic malformation in kidney

- ▶ Polycystic kidney disease
 - ▶ Autosomal recessive
 - ▶ Autosomal dominant
 - ▶ As part of a multi-system genetic condition
- ▶ Medullary cysts
- ▶ Glomerulocystic disease
- ▶ Multicystic dysplastic kidney disease
- ▶ Simple renal cysts
- ▶ Multilocular cysts
- ▶ Acquired cystic kidney disease

Figure 1 Kidneys 10 cm in length (normal around 5.5 cm). Loss of normal cortico-medullary differentiation. Hyperechogenic medulla, hypoechogenic areas in keeping with small cysts. Some focal increase in echogenicity in keeping with nephrocalcinosis.

Figure 2 Liver US shows variable echogenicity in keeping with fibrosis.

Genetic disorders associated with renal cysts

- ▶ Bardet-Biedl syndrome
- ▶ Brachio-oto-renal syndrome
- ▶ Ellis-van Creveld syndrome
- ▶ Jeune syndrome
- ▶ Meckel-Gruber syndrome
- ▶ Tuberous sclerosis
- ▶ Von Hippel-Lindau syndrome

TREATMENT

Cardiovascular management in this case

The infant was hypertensive. By 7 months of age she was on triple antihypertensive therapy of atenolol, amlodipine and enalapril (which was later changed to doxazocin).

Gastroenterology management in this case

The gastroenterology team became involved at age 3.5 years. On initial assessment a 6 cm liver edge and 5 cm spleen were palpable. Prominence of superficial abdominal veins, palmar erythema and facial plethora suggested the presence of portal hypertension. Liver function tests and coagulation remained within normal limits. She was

Figure 3 A nodular liver with broad bands of fibrous tissue containing numerous bile duct profiles. x4 power, the stain is a trichrome stain.

kept under annual review by this team in anticipation that hepatic dysfunction and portal hypertension might evolve over time.

At age 4 years an ultrasound scan showed changes compatible with hepatic fibrosis (as shown in figure 2) and splenomegaly with length of 11 cm. The portal vein was reported to be normal. Her portohepatic status was monitored with annual US. Upper gastrointestinal endoscopy and liver biopsy were also performed at age 4 years. The endoscopy identified grade 1 oesophageal varices and portal hypertensive gastropathy. The latter finding is where the gastric mucosa becomes more congested, hyperaemic and prone to bleeding as a result of the increased venous back pressure.

The biopsy showed features consistent with congenital hepatic fibrosis, without dilatation of the biliary tree and sinusoidal changes in keeping with portal hypertension. Figure 3 shows the fibrotic nature of the patient's liver on a pathology slide.

From about age 5, persistent borderline pancytopenia was noted which was thought to be the result of hypersplenism.

Following a self-limiting episode of haematemesis that occurred during a probable viral gastroenteritis, endoscopy was repeated at age 7. Grade 1 oesophageal varices were again noted in conjunction with portal hypertensive gastropathy.

Renal management in this case

Figure 4 (graphs A and B) illustrate deterioration of renal function towards end-stage despite maximal medical management with optimal blood pressure control. The following medications were introduced as a result of this:

- ▶ Iron
- ▶ 1-alpha-calcidol
- ▶ Sodium bicarbonate
- ▶ Cinacalcet
- ▶ Dialyvit (multivitamin for children with renal impairment)
- ▶ Erythropoietin

The decision was made to proceed to living-related renal transplant (from father) at age 7.8 years. This was done as a pre-emptive measure before the requirement for dialysis.

Several issues were debated in the lead up to transplantation:

- 1) Whether to remove one or both of the patient's enlarged kidneys to make space, given that the donor graft was an adult size and there was combined enlargement of kidneys, liver and spleen. It was postulated that removal of native kidneys would potentially contribute to postoperative morbidity. The fact that this patient had ascites was felt to be an advantage as this would have helped increase the capacity of the abdominal space.
- 2) Whether to perform a combined kidney/liver transplant in anticipation that with progressive hepatic disease, a liver transplant may later become necessary and would then be technically more challenging given the previous laparotomy and ongoing immunosuppressant therapy. Following transplant investigation at the paediatric liver unit, the absence of hepatobiliary complications such as biliary dilatation, cholangitis, loss of synthetic function or uncontrolled portal hypertension mitigated against this.

Although there was evidence of ongoing portal hypertension at this point, this had not so far posed a major problem. There was evidence of hypersplenism, but the

blood counts had not reached significantly low levels. As mentioned there had been one episode of upper gastrointestinal bleeding which had settled spontaneously. Endoscopy performed recently had identified only grade 1 oesophageal varices which did not require banding. This situation had remained static in comparison to a previous endoscopy performed 3 years earlier.

It was felt that problems arising later as a result of further evolution in portal hypertension might be controlled through variceal banding or a 'TIPS' shunt (transjugular intrahepatic porto-systemic shunt) as an alternative to liver transplant. TIPS involves the creation of an artificial channel within the liver that connects the incoming portal vein with the outgoing hepatic vein thus bypassing the liver. This procedure results in a significant change in blood flow in this region. Potential risks associated with this include hepatic ischaemia and encephalopathy which may result from a shunting of nitrogen based products from the portal to the systemic circulation. On the basis of the extent of portal hypertension and risk-benefit balance, this was not felt to be warranted at the time leading up to the renal transplant.

In view of these considerations, the decision was made for isolated renal transplant to be performed into the

Figure 4 Graphs A and B demonstrate the steady decline in renal function in terms of serum creatinine and glomerular filtration rate respectively.

Figure 5 Microscopic staining of sections from explanted graft kidney. (A) The infarcted parenchyma shows necrosis of the renal tubules in the affected area together with some signs of longstanding ischaemic damage including calcification (large picture: H&E x2. Insert left: H&E x10. Insert right H&E x4); (B): thrombus with recanalisation in a large hilar vessel highlights the acute on chronic vascular compromise. (H&E x2 large picture. Inserts: Elastic van Gieson x2 and H&E x10).

retroperitoneal space of the right iliac fossa with no prior organ removal.

Shortly after an uncomplicated kidney transplant the patient was transferred to intensive care unit where a significant drop in the urine output was noted. An ultrasound scan was consistent with reduced cortical perfusion and high perfusion index in combination with patent renal vessels. A clot was noted within the renal pelvis.

The patient was immediately taken back to theatre for re-exploration. This confirmed the clinical suspicion of a compartment syndrome. This was defined by severe venous congestion in the absence of vascular thrombosis and had resulted from excessive tension during muscle closure. This had led to acute organ ischaemia, diffuse oozing and, in this particular case, to pelvic haemorrhage and clotting within the collecting system. At this point, the kidney was still deemed viable. The clot was evacuated, biopsies

were taken and a partial closing of the abdominal wall was carried out to avoid any further tension. The biopsies suggested ischaemic necrosis.

In the following weeks, there were several episodes of suspected sepsis associated with fever and raised inflammatory markers. Liver function tests remained stable. These episodes were covered with broad-spectrum antibiotics. Necrosis of the transplanted kidney may have contributed to these symptoms and signs as all cultures were negative until *Klebsiella pneumoniae* was finally isolated on a blood culture taken 6 days before nephrectomy. This was treated with ciprofloxacin.

Unfortunately the ischaemic injury, complicated by infection proved to be irreversible with primary non-function. This led to the necessity for transplant nephrectomy 4 months after the transplant. Immunosuppressant therapies were stopped following nephrectomy.

At explantation, a perinephric abscess was debrided. Pathological examination of the graft confirmed extensive necrosis. Some of these changes are displayed in figure 5A,B.

In the days following nephrectomy although the creatinine levels gradually rose above 200 µmol/l, she did not require haemodialysis.

Approximately 2 weeks after the nephrectomy, she became acutely confused and disorientated. Ammonia was 108 µmol/l (ref 20–40 µmol/l), C reactive protein 16 mg/l, urea and electrolytes were stable. Blood pressure was within normal limits. Blood gas showed normal pH with no base deficit. Calcium, magnesium and glucose were normal, lactate 1.7 mmol/l, CT head scan was normal, EEG showed diffuse slow wave activity.

This change in mental status was thought to represent hepatic encephalopathy related to porto-systemic shunting. She was transferred to the regional paediatric liver centre. In view of deterioration in liver function, the presence of encephalopathy and failure of the renal graft, she was placed on the waiting list for combined liver/kidney transplant, which took place 1 month later.

OUTCOME AND FOLLOW-UP

Postcombined transplant she has made a good recovery. Renal and liver function tests have normalised. Spleen size is steadily reducing as is the hypersplenism. There have been no rejection episodes to date. This was verified on a transplant liver biopsy done as a routine procedure 1 year post-transplant. An upper gastrointestinal (GI) endoscopy performed at the same time showed no signs of portal hypertension.

She has managed to return to a near normal life. She has regular follow-up in the combined renal/GI clinic.

Current therapy:

- ▶ Mycophenolate mofetil
- ▶ Tacrolimus
- ▶ Prednisolone
- ▶ Amlodipine
- ▶ Alfacalcidol
- ▶ Ursodeoxycholic acid.

DISCUSSION

In this case, there was no evidence during the antenatal period of the presence of ARPKD. The first indication of this came when the infant developed respiratory distress in the immediate postnatal period secondary to pneumothorax. In a retrospective review by Capisonda *et al*, this scenario in ARPKD is considered to be a poor prognostic marker for the patient¹ being consistent with the more severe neonatal phenotype of the condition. This is associated with pulmonary hypoplasia resulting from oligohydramnios. In this patient, these respiratory issues were not persistent and settled after the first few days. There was also absence of a history of oligohydramnios, features of Potter's Facies or neonatal renal malfunction.

Despite early neonatal diagnosis and aggressive management of hypertension, steady deterioration in renal function ensued in this patient, necessitating combined liver and kidney transplantation at the age of only 7 years.

During discussions relating to transplantation and the presence of significant organ enlargement, the decision was made to proceed to renal transplant without prior nephrectomy, as the risks of this operation were thought to outweigh its benefits.

Following transplant, pressure around the graft kidney accumulated resulting in a compartment syndrome which is a well recognised and documented complication during the early post-transplant period. This is associated with tension created in closing the muscle overlying the graft.^{5–7} This resulted in irreparable damage to this within a short period of time. Had nephrectomy been performed before transplantation, pressure build up may have been averted or at least minimised. There is currently no way of accurately predicting those at risk of this complication other than relying on subjective impressions of the space available within the abdominal cavity on scans and clinical inspection.

In a case series of 10 patients published in 2006⁸ dealing with the severe neonatal form of the disease early pre-emptive nephrectomy within the first 18 months of life was performed. These infants were then established on peritoneal dialysis and optimised feeding. They proposed that early nephrectomy with the resultant reduction in mass effect minimised respiratory compromise and improved feeding and nutrition. They found that this approach minimised morbidity and increased success of renal transplantation some years later. Different units may therefore be taking quite different approaches in the management of this condition.

In the initial transplant investigation in this case, combined liver and kidney transplantation had been considered. However, this was decided against on the grounds that the synthetic function of the liver was preserved, there had been no episodes of cholangitis or complications related to uncontrolled portal hypertension. However, shortly after the first transplant, probably accelerated by a series of insults and stressors in the post-transplant period, decompensation in hepatic status occurred necessitating a combined transplant. These criteria therefore are perhaps not a reliable means of determining those in whom a combined transplant may be appropriate.

The proportion of ARPKD cases who have clinically significant congenital hepatic fibrosis varies widely. This condition is progressive. A study followed up 14 patients receiving renal transplants for ARPKD in a unit in Minnesota between 1972 and 1998.⁹ Over a mean follow-up period of 14.5 years, 79% of the group went on to develop complications resulting from congestive hepatic failure (CHF), in particular portal hypertension, cholangitis and hepatic failure. Of a total death rate of 36% during the period of follow-up, 80% of these deaths were attributable to CHF complications, especially sepsis related to cholangitis. This team therefore recommended consideration of earlier liver transplant in the kidney transplanted population. This may ultimately be extrapolated to the situation of combining the two organ transplants in the first procedure.

This case outlines the potential complexity of this condition and the complications associated with surgical intervention. Improvements in survival rates for the more severe forms of ARPKD through renal transplantation may lead to increasing numbers experiencing later problems as a result of liver complications of CHF. Further work to determine the best management strategy is required.

Meanwhile, having identified the genetic mutations associated with ARPKD and the gene product involved, research is also ongoing into other treatment options including the use of vasopressin V2 receptor antagonists¹⁰ and tyrosine kinase inhibitors¹¹ which may interrupt the process of cystogenesis in the first place and so lead to a very different strategy for managing this condition in the future.

Learning points

- ▶ In ARPKD, there can be a wide variation in phenotype with variable effects on kidney and liver function and multi-disciplinary management must be tailored to the individual patient.
- ▶ There is still relatively little information available on long-term outcomes in transplanted patients and the surgical management of this condition is still evolving. A consensus opinion on the optimal management strategy is yet to be reached.
- ▶ Where the abdominal cavity is significantly encroached upon by the combined enlargement of kidneys, liver and spleen, nephrectomy may be warranted to create adequate space for the donor kidney.
- ▶ After managing renal compromise through transplant, the hepatic complications are likely to become more significant over time. Therefore careful consideration should be given to the merits of performing combined renal and liver transplants in this condition.

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