Clinical Observations

A study of long-term morbidity associated with autosomal recessive polycystic kidney disease

Bilal Jamil1, Lawrence P. McMahon1, Judith A. Savige2, Yan Y. Wang2 and Rowan G. Walker1

1Department of Nephrology, C/- Post Office, Royal Melbourne Hospital, and 2University of Melbourne, Department of Medicine, Austin and Repatriation Medical Centre, Heidelberg, Victoria, Australia

Introduction

Blyth and Ockenden in 1971 [1] separated autosomal recessive polycystic kidney disease (ARPKD) from other cystic diseases, describing four sub-groups (perinatal, neonatal, infantile and juvenile) on the basis of age-at-presentation, clinical symptoms and pathological findings. They speculated that different genes might be responsible for each group as affected children in one family always had similar disease. Subsequent reviews, however, showed marked clinical variability within a single kindred which appeared to refute this hypothesis [2,3]. Zerres et al. [4] mapped the ARPKD gene locus to a 13-cm region of chromosome 6p 21.cen in a cohort of families mostly with milder phenotypes of the disease. Guay-Woodford et al. [5] showed that the severe perinatal form of ARPKD also mapped to the same chromosome. Taken together, these studies suggest there is a single ARPKD gene.

Although the clinical spectrum of ARPKD is widely variable, a child commonly presents during the first month after birth with enlarged kidneys [6–9] which can occasionally complicate delivery [1]. Severely affected infants may display pulmonary hypoplasia, spontaneous pneumothoraces and Potter’s facies.

Both renal and hepatic abnormalities are present in all affected children although there is a predominance of renal disease in younger children and of hepatic disease in older children and adolescents [10]. Loss of concentrating ability of the kidney is frequent before advanced renal insufficiency has developed [8]. Recurrent urinary tract infection is common, and proteinuria and haematuria may be present. Creatinine clearance improves early in life and remains stable for several years before declining progressively during adolescence [6]. Hypertension frequently develops early in life, but usually regresses. Congenital hepatic fibrosis is invariably present but only occasionally do hepatic symptoms predominate: usually from portal hypertension and hypersplenism. Hepatocellular decompensa-

Case studies

Case 1. The first child of a non-consanguineous marriage, was diagnosed with enlarged kidneys when 6 days old. An intravenous pyelogram (IVP) showed polycystic kidneys. By the age of 4 years she had developed hypertension and was found to have hepatosplenomegaly. A liver biopsy showed features consistent with congenital hepatic fibrosis. She developed hypersplenism at the age of 5 years. A year later, a barium swallow demonstrated oesophageal varices and a splenoportogram documented portal hypertension. At 13 years, a left distal splenorenal shunt was performed for recurrent episodes of severe gastrointestinal haemorrhage but her varices continued to bleed necessitating sclerotherapy. Splenectomy was required for persistent thrombocytopenia at the age of 14 years.

By 16 years she had developed end-stage renal failure and continuous ambulatory peritoneal dialysis (CAPD) was initiated. After 1 year on dialysis she received a cadaveric renal transplant. This failed after 6 years and haemodialysis was commenced. At 25 a cholecystectomy was performed for cholecystitis. Recurrent
episodes of biliary sepsis followed and an Endoscopic
Retrograde Cholangiopancreatogram (ERCP) showed
markedly dilated bile ducts consistent with Caroli’s
disease. She received her second renal transplant from
her father which continues to function well after 2
years.

Case 2. Younger brother of case 1, he had bilateral
enlarged kidneys and hepatosplenomegaly at birth.
The ultrasound and computed tomography (CT) scan of
liver and spleen were consistent with the diagnosis
of congenital hepatic fibrosis and Caroli’s disease. He
developed hypertension when 3½ years old and suffered
from haematemesis due to oesophageal varices from
the age of 4 years.

From that age, he also suffered from recurrent
vasculitis (polyarteritis nodosa) involving skin, oral
mucous membranes and small bowel. His vasculitis
responded well to steroids, however, relapses occurred
when the dose of prednisolone fell below 10 mg/day.
These relapses resulted in loss of his distal fingers and
 toes at the age of 4 years and sections of his small
intestine at 14 and 16 years. He required a splenectomy
at the age of 14 years. Two months prior to his death
he had near total small bowel resection due to severe
vasculitis and gangrene. He required steroids for vascu-
litis continuously from the age of 4 years until his
death from septicaemia at the age of 20 years. His
renal function was only ever mildly impaired with a
serum creatinine less than 0.14 mmol/l.

Case 3. Younger sister of cases 1 and 2, she had
bilateral enlarged kidneys and hepatosplenomegaly at
birth. She developed hypertension when 2 years old.
IVP at the age of 5 years showed large kidneys with a
linear streaky pattern of contrast collection in the
parenchyma. Her abdominal ultrasound showed an
enlarged liver and spleen with evidence of portal hyper-
tension. She was pancytopenic from the age of 12 years
and suffered frequent episodes of epistaxis associated
with thrombocytopenia and high blood pressure.
Gastrointestinal bleeding was never observed. She
reached end-stage renal failure at the age of 13 years
when CAPD was commenced. She has been on dialysis
now for 4 years without any significant complications
or progression of liver disease.

Case 4. A 28-year-old woman with end-stage renal
failure was referred for ongoing management of renal
failure. She was known to have portal hypertension
and hypersplenism. Hepatomegaly had been noted at
birth. At age 3 months she had an IVP which showed
large lobulated kidneys with marked tubular ectasia.
Haematemesis occurred at 8 years of age. Ultrasound
demonstrated portal hypertension with a large and
densely fibrotic liver and marked splenomegaly. Varices
were seen on oesophagoscopy. Her renal function
gradually deteriorated requiring initiation of haemo-
dialysis at the age of 28 years. Shortly after dialysis
was commenced she developed frequent episodes of
haematemesis which were successfully controlled after
multiple sessions of sclerotherapy. She has been stable
on dialysis for 3 years and awaits a cadaveric transplant.

Case 5. A 24-year-old man was referred for manage-
ment of chronic renal failure secondary to polycystic
kidneys. Soon after birth he developed severe respira-
tory distress secondary to bilateral spontaneous pneum-
othoraces requiring intercostal drainage. Bilateral
abdominal masses were also discovered. An IVP was
performed 14 days after birth which showed bilateral
enlarged kidneys with linear streaky pattern of contrast
collection in the parenchyma suggestive of ARPKD.
Films repeated at 4 months and 9 years of age showed
similar features. Hypertension was documented at the
age of 9 years. His renal function, normal at this stage,
gradually deteriorated and chronic haemodialysis was
commenced at the age of 26 years. At the age of 28
years he received a cadaveric renal allograft. Currently
on ultrasound his liver is bulky but otherwise normal,
there is no evidence of portal hypertension, his liver
function tests have been normal. There have been no
episodes of gastrointestinal bleeding or jaundice. For
these reasons a liver biopsy has not been performed.
His parents are healthy with normal kidneys on
ultrasound.

Case 6. A 2-year-old boy was referred to a nephrolo-
gist for bilateral loin masses. He was born 3 weeks
preterm and had respiratory distress at birth. He was
hypertensive and had impaired renal function. An IVP
was consistent with ARPKD. A liver biopsy showed
congenital hepatic fibrosis and Caroli’s disease. He
reached end-stage renal failure at the age of 8½ years
when CAPD was commenced. After 5 months on
CAPD he received a cadaveric renal transplant. Nine
years post-transplant his renal function is stable with a
creatinine of 0.23 mmol/l. He has mild hypersplenism
but has never had a gastrointestinal haemorrhage.

Case 7. A 20-year-old woman presented during her
first pregnancy with recurrent urinary tract infections.
She was also found to have splenomegaly. She had
eight episodes of Escherichia coli urinary tract infection
during her pregnancy, each episode associated with
pancytopenia. There was no family history of renal or
liver disease. She was normotensive, and had normal
liver and kidney function. Her abdominal ultrasound
showed bilaterally enlarged kidneys and hepatospleno-
megaly. The portal vein was of normal diameter. An
IVP performed after she was delivered of her child
showed features of ARPKD. Liver biopsy showed
features of Caroli’s disease and congenital hepatic
fibrosis. A repeat abdominal ultrasound 2 years later
demonstrated signs of portal hypertension. Neither her
liver nor renal disease have progressed since her dia-
gnosis 3 years ago.

Gene linkage studies

Linkage to the locus for ARPKD was studied in three
families (A, B and C, Figure 1) using the microsatellite
markers, D6S295 and D6S272, which are located
within 13 cM of the ARPKD locus [4].

Genomic DNA was extracted from peripheral blood
leucocytes using conventional techniques. One hundred
nanograms of the 5’ primer were labelled by incubation
Long-term outcome for ARPKD

Fig. 1. Linkage studies in families A, B and C at locus for ARPKD. The figure shows haplotypes demonstrated with D6S295 (on top) and D6S272. None of the affected individuals is homozygous for an allele from a consanguineous relationship. There is a recombination event in the second offspring in family A.

with 1 μl 10 × kinase buffer (Progen), 1 unit of T4 polynucleotide kinase (Progen) and 0.5 μCi [32P] ATP (Amersham) in a total volume of 10 μl at 37 °C for 30 min. The enzyme was then denatured at 65 °C for 15 min.

DNA was amplified in a 10-μl reaction volume containing 100 ng DNA, with 50 μg each of 5′ (radio-labelled) and 3′ primers, 2.5 mM MgCl2 (Bresatec), 2.5 mM dNTP (Pharmacia), 1 μl of 10 × Taw polynucleotide buffer (Bresatec) and 1 unit of Taq polymerase (Bresatec). The mixture was subjected to an initial denaturation of 94 °C for 5 min, followed by 30 cycles of 94 °C for 1 min, 55 °C for 1 min and 72 °C for 1 min, with a final cycle of 94 °C for 2 min and 72 °C for 5 min.

The amplified products were then separated on a 7% denaturing polyacrylamide sequencing gel. The results were interpreted independently by two investigators.

Results

The families are too small for linkage to the locus for ARPKD to be demonstrated individually. A recombination event was demonstrated only in family A with D6S272 (Figure 1). The results indicate that consanguinity was unlikely to account for the disease in these families.

Discussion

Children with ARPKD are now being offered renal replacement therapy (RRT). Although reports on the outcome of such treatment are few, it is generally believed that patients are at high risk; that after initiation of dialysis or a successful renal transplant, hepatic complications gradually progress and ultimately dominate the clinical picture. These complications are difficult to manage, and a variety of recommendations including prophylactic porta-caval shunt, splenectomy [12], or combined liver/kidney transplantation have been suggested.

The clinical course of seven adult patients with ARPKD is documented. The diagnosis in these patients was based on clinical evidence together with a normal renal ultrasound in both parents. Case 5 has few features of liver disease, however, his presentation at birth with enlarged kidneys which subsequently regressed in size, and more importantly a normal renal ultrasound of parents support the diagnosis of ARPKD [12,13]. The possibility of autosomal dominant polycystic kidney disease due to a spontaneous mutation is unlikely.

Five of the seven patients remain on RRT. Currently, two are being dialysed and three have received a renal transplant, with survival demonstrated up to 11 years (Table 1). Five patients had portal hypertension but only two had recurrent bleeding from oesophageal varices. In both cases (1 and 4), splerotherapy appears to have been a successful therapeutic option. The presence of portal hypertension did not necessarily predict gastrointestinal haemorrhage (cases 2, 3 and 7) and in all cases synthetic hepatic function and transaminase activity has been intact. Hypersplenism occurred in six patients and so far splenectomy has been required in two (cases 1 and 2). Caroli’s disease has been documented in four patients (cases 1, 2, 6 and 7) although only one (case 1) had recurrent cholangitis.

The reports of long-term follow-up of children with ARPKD on RRT do not provide convincing evidence for prophylactic porta-caval shunt or combined liver/kidney transplant. Roy et al. [14] have recently reported long-term follow-up of 52 children with ARPKD. Of eight patients who received RRT, six had a renal transplant. Three died soon after the surgery, although in none was death due to liver disease. Three had a functioning renal allograft and two were on dialysis. One patient on haemodialysis had recurrent portal-systemic encephalophathy and was being considered for a combined liver/kidney transplant. Another patient, aged 30 years, had intermittent haematemesis since the age of 28 years. A third patient had ultrasound evidence of gastro-oesophageal varices, which had not bled. Survival on RRT was reported to be from 2 to 8 years. McGonigle et al. [15] reported three cases of ARPKD, two of whom underwent renal transplantation. One of these developed haematemesis which was treated with repeated sclerotherapy. In the other patient a lienorenal shunt and splenectomy were performed before a renal transplant. A prophylactic porta-caval shunt was recommended prior to transplantation. A good outcome was achieved in both cases.

In the current study, six patients were treated for hypertension (not case 7) before developing renal impairment. It regressed completely in two patients (cases 1 and 4). This is well described, however, the mechanism remains unexplained [8]. Case 7 presented at the age of 20 years with no relevant past or family history which is most unusual as individuals presenting in adolescence generally have either personal history suggestive of ARPKD [16–18] or a positive family history [2,19].

The relevance of genetic testing remains unclear. Although localized to chromosome 6, the specific gene has not been identified. No additional clinical information was obtained from the families consented to genetic analysis and at this stage, testing would...
Table 1. Features of patients with autosomal recessive polycystic kidney disease

<table>
<thead>
<tr>
<th>Family A</th>
<th>Family B</th>
<th>Family C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1: 27, F</td>
<td>Case 2: Died 20, M</td>
<td>Case 3: 18, F</td>
</tr>
<tr>
<td>Case 4: 31, F</td>
<td>Case 5: 30, M</td>
<td>Case 6: 18, M</td>
</tr>
<tr>
<td>Case 7: 23, F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>Perinatal problems</th>
<th>Hypertension (&gt; 150/100)</th>
<th>Kidney size in cm</th>
<th>Renal calcification</th>
<th>Renal failure</th>
<th>Renal transplant</th>
<th>Hepatomegaly</th>
<th>C.H.F.</th>
<th>Caroli's disease</th>
<th>Portal hypertension</th>
<th>Hypermegism</th>
<th>Bleeding varices</th>
<th>Predominant presenting symptoms</th>
<th>Other problems</th>
<th>Survival on RRT — years</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 days</td>
<td>—</td>
<td>+(4 years)</td>
<td>Enlarged</td>
<td>—</td>
<td>+CT</td>
<td>CAD (17 years) [6 years]</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+ (4 years)</td>
<td>+Spinectomy (14 years)</td>
<td>—</td>
<td>Severe persistent Hepatic portal HT</td>
<td>Recurrent cholangitis</td>
</tr>
<tr>
<td>1 month</td>
<td>—</td>
<td>+(3½ years)</td>
<td>Enlarged 12 × 12 (2 years)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1 month</td>
<td>—</td>
<td>+(2 years)</td>
<td>11.6 × 11.5 (3 months) 6.6 × 7.2 (28 years)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3 months</td>
<td>—</td>
<td>—</td>
<td>11 × 11.5 (9 years) 9.2 × 9.8 (16 years)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1 day</td>
<td>—</td>
<td>Bilat. spontaneous pneumothoraces + (9 years)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2 years</td>
<td>—</td>
<td>+(2 years)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20 years</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Notes: Bilat., bilateral; CAD, cadaveric; CT, CT scan; ERCP, Endoscopic Retrograde Cholangiopancreatogram; LRD, living related donor; RRT, renal replacement therapy; US, Ultrasonography; ( ), age at diagnosis/detection; [ ], duration of a functioning graft.
Long-term outcome for ARPKD seems more appropriately performed for research purposes.

Cases 1 and 3, both females, reached end-stage renal failure at the ages of 16 and 15 years, respectively but their brother, case 2, had only mild renal impairment: his serum creatinine was 0.10 mmol/1 before his death at the age of 20 years. He had been on prednisolone long-term for his vasculitis. Recently methylprednisolone has been shown to preserve renal function in mice and rats with severe forms of inherited polycystic kidney disease [20]. Although this might have therapeutic potential, human data is currently lacking.

In our experience, liver disease did not appear to progress rapidly after initiation of renal replacement therapy and did not subsequently present a clinical problem (cases 3, 5 and 6). When it occurs, recurrent bleeding appears to be controllable with sclerotherapy. Cholangitis is not a significant problem. We believe that renal transplantation is appropriate for patients with ARPKD and that prophylactic porta-caval shunting or combined liver/kidney transplantation is unnecessary.

References


Received for publication: 18.4.98
Accepted in revised form: 3.8.98