Autosomal recessive polycystic kidney disease

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Abstract. Autosomal recessive polycystic kidney disease (ARPKD) is a rare inherited disorder which usually becomes clinically manifest in early childhood. With increasing knowledge and improving diagnostic techniques it has become evident that the spectrum of ARPKD is much more variable than was previously thought. Presentation of ARPKD at later ages and survival into adulthood is well known. Diagnostic criteria, clinical course, genetics and differential diagnosis of ARPKD are presented.

Key words: autosomal recessive polycystic kidney disease; clinical picture; congenital hepatic fibrosis; genetics

Introduction

Many important papers about this subject have been published which give a comprehensive overview [1-19]. Diagnostic criteria, clinical course, genetics and differential diagnosis of autosomal recessive polycystic kidney disease (ARPKD) are presented here and clinical data of systematic studies are summarized.

Pathoanatomical features of ARPKD

Renal involvement is invariably bilateral and largely symmetrical. The cut surface demonstrates the cortical extension of fusiform or cylindrical spaces arranged radially throughout the renal parenchyma from the medulla to the cortex. The epithelium shows no signs of compression. ARPKD is invariably associated with a generalized portal and interlobular fibrosis of the liver accompanied by biliary duct hyperplasia and small distal portal vein branches.

Changing phenotype with prolonged survival

The occasionally reported prolonged survival of persons with ARPKD (up to the sixth decade) indicates that the quantitative extent of cyst formation is variable, as Blyth and Ockenden [5] have postulated [20]. The most common manifestation of ARPKD is the perinatal form, with enlarged kidneys in the neonate. The extent of hepatic fibrosis seems to increase with prolonged survival in cases with milder renal changes. There are cases with onset in early childhood showing severe liver involvement, as well as cases with onset of clinical symptoms in adulthood without symptoms of portal hypertension. With respect to the differential diagnosis, one must bear in mind that the morphological picture of collecting duct ectasia loses its uniformity with increasing age. The cysts become non-uniform and larger cysts begin to compress the renal pelvis.

Changes in the patho-anatomical and radiological picture have been observed which resemble those of autosomal dominant polycystic kidney disease [14].

Incidence

The exact incidence of ARPKD is unknown. Figures range from 1:6000–1:14 000 [21] to 1:55 000 [22]. We have made a rough estimate that the incidence is ~1:40 000 [7]. Because of the special genetic situation in Finland, the figure published by Kääriäinen et al. [13] of 1:1000 is perhaps not representative for other countries.

Clinical features and course

Table 1 summarizes the results of systematic studies on the clinical picture in ARPKD. It has to be mentioned that these studies represent selective study groups of children most often from departments of paediatric nephrology who in most cases survived the neonatal period. The most common initial features are palpable kidneys and an enlarged liver, followed by respiratory
failure, hypertension and urinary tract infections. The diagnosis can usually be made in early childhood. Some cases have been suspected or diagnosed by fetal ultrasonography. Oligohydramnios due to poor renal output can be present and can cause the ‘Potter-sequence’. The criteria for impairment of renal function differed in the published studies. Renal function was decreased in about half of the patients while 10–29% of the patients reached end-stage renal failure. A total of 69% of children in our systematic study [19] had a kidney length above +2 SD. A comparison of the kidney length of first and last observation did not show an increase in size with decreasing renal function or increasing age. Hypertension requiring drug treatment was found in 61–70% in four studies and 100% in one study (see Table 1). Hypertension is one of the major clinical problems in medical care of patients with ARPKD. Thirty-one per cent of patients treated with antihypertensive medication in our study [19] were still hypertensive according to the US task force definition of severe hypertension. Urinary tract infections occurred in 30–43% of patients. Growth retardation could be observed in 25% in our study, which correlated with renal function [19]. Clinical signs and ultrasonographic signs of hepatic fibrosis were detected in 29–61%. Death rates in the first year of life differed, and among those patients assessed by departments of paediatric nephrology were between 9 and 24%. We observed a statistically significant gender difference, with a more pronounced progression in girls. Respiratory difficulties probably resulting from enlargement of the kidneys (particularly diaphragmatic elevation and hypoplasia of the lungs) cause death usually within hours after birth. The prognosis of those who survive the first months of life is much better. With prolonged survival renal failure and hepatic involvement become life-threatening. Clinically, portal hypertension due to hepatic fibrosis often predominates. These children sometimes present with gastrointestinal bleeding from varices or hepatomegaly due to congenital hepatic fibrosis. Liver function itself, however, is usually normal.

**Differential diagnosis**

The most important differential diagnosis is autosomal dominant polycystic kidney disease (ADPKD), which can be indistinguishable from ARPKD. In these cases the demonstration of cystic changes in one parent enables a definite diagnosis of ADPKD to be made. We follow the opinion of Ogborn [23], who recently stated ‘Perhaps the single most useful investigation in the evaluation of a child with early onset of cystic renal disease is ultrasound of the parents... Thus a negative ultrasound of both parents reduces the probability of...

### Table 1. Autosomal recessive polycystic kidney disease: summary of clinical findings of systematic studies (modified from [19])

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patient (n)</th>
<th>Age at diagnosis</th>
<th>Main initial presentation</th>
<th>Renal function</th>
<th>Hypertension</th>
<th>Urinalysis</th>
<th>Growth</th>
<th>Liver symptoms</th>
<th>Survival rate</th>
<th>Death rate in the first year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cole et al. (1987) [10]</td>
<td>17</td>
<td>(n = 18 for analysis)</td>
<td>72% enrolled kidneys</td>
<td>35% GFR &lt; 40 ml/min</td>
<td>29% ESRD</td>
<td>39% UTI</td>
<td>56% proteinuria</td>
<td>29% portal hypertension</td>
<td>1 year: 79%</td>
<td>12%</td>
</tr>
<tr>
<td>Kääriäinen et al. (1988) [13]</td>
<td>73</td>
<td>6% ≤ 1 year</td>
<td>72% enrolled kidneys</td>
<td>81% GFR &lt; 90 ml/min</td>
<td>6% ≤ 1 year</td>
<td>50% proteinuria</td>
<td>1 pat. &lt; 3.5 SD</td>
<td>25% (enlarged liver)</td>
<td>10 years: 51%</td>
<td>75%</td>
</tr>
<tr>
<td>Kaplan et al. (1989) [15]</td>
<td>55</td>
<td>10% &gt; 1 year</td>
<td>48% palpable kidneys</td>
<td>58% 'elevated' SCR</td>
<td>67% drug treatment</td>
<td>56% (inclusion criterion)</td>
<td>1 pat. &lt; 3.5 SD</td>
<td>50% (enlarged liver)</td>
<td>5 years: 46%</td>
<td>24%</td>
</tr>
<tr>
<td>Gagnadoux et al. (1989) [16]</td>
<td>33</td>
<td>22% &gt; 1 year</td>
<td>11% enlarged liver</td>
<td>8% respiratory failure</td>
<td>21%ESRD</td>
<td>65%</td>
<td>1 pat. &lt; 3.5 SD</td>
<td>47% (splenomegaly)</td>
<td>10 years: 51%</td>
<td>9%</td>
</tr>
<tr>
<td>Zerres et al. (1996) [19]</td>
<td>115</td>
<td>72% &lt; 1 month</td>
<td>15% liver symptoms</td>
<td>24% GFR &lt; 80 ml/min</td>
<td>10%ESRD</td>
<td>67% (measured)</td>
<td>1.39</td>
<td>48% (splenomegaly)</td>
<td>1 year: 94% (m)</td>
<td>9%</td>
</tr>
</tbody>
</table>
a diagnosis of ADPKD to the level of a spontaneous mutation'. Meckel syndrome and kidney involvement in Bardet–Biedl syndrome are important differential diagnoses but do normally show larger cysts. Other conditions such as nephroblastosis, bilateral Wilms tumor, pyelonephritis, transient nephromegaly, radio-contrast nephropathy and glomerulonephritis may mimic ARPKD.

Renal cystic changes are frequently found in patients with congenital hepatic fibrosis. This coincidence could be explained if cases of mild forms of ARPKD were interpreted as congenital hepatic fibrosis. In this view, most (if not all) cases with classical autosomal recessive congenital hepatic fibrosis without further malformations should be regarded as mild manifestations of ARPKD with only slight renal involvement. Not all changes microscopically diagnosed as congenital hepatic fibrosis (CHF), however, are manifestations of ARPKD since similar changes can be found in several conditions such as Meckel syndrome, Jeune syndrome, different short rib-polydactyly syndromes and Ivemark syndrome [see 7]. As has been documented recently, congenital hepatic fibrosis has been observed in rare cases with ADPKD as well [24]. A family history leads to the definite diagnosis of ADPKD in these cases. The existence of CHF in different diseases indicates a heterogeneous aetiology of congenital hepatic fibrosis. It is still a debatable question whether the liver involvement is identical in the different conditions. Since hepatic pathology is of special significance for the classification of cystic kidney diseases, the liver should always be examined. Gross cystic dilatation of the intrahepatic biliary tree is usually called Caroli disease. The frequent association with ARPKD is well established. Presumably ARPKD and Caroli disease are a closely overlapping syndrome in which an abnormal developmental involvement on different levels of the biliary tree due to the same pathogenetic mechanism might result in two different spectra or stages of a single disease [25].

When should the diagnosis of ARPKD be made in adults?

To establish the positive diagnosis of ARPKD in a patient with polycystic kidneys can be difficult. The most important finding is a negative family history and a normal ultrasound in parents (who should be >30 years old) of patients with PKD. A negative family history of a patient with PKD, however, does not prove the diagnosis because of the possibilities of illegitimate paternity and spontaneous mutation of ADPKD. The diagnosis is reliable in those cases with negative family history and symptoms of portal hypertension. Parental consanguinity and normal parental ultrasound are also important arguments for the diagnosis of ARPKD. In all the other cases only a liver biopsy enables the diagnosis to be made with confidence. This is needed, for example, in genetic counselling and as a obligatory prerequisite for prenatal diagnosis in families with CHF. But even then, an autosomal dominant form cannot be completely excluded, since we know that CHF can be found in rare cases of ADPKD [23]. The theoretical possibility of a germ cell line mosaicism has to be considered as well. An exact diagnosis will be possible in the future when the mutation on the DNA level can be demonstrated directly.

Course of ARPKD in siblings

In a recent study on the clinical course of 42 children out of 20 sibships with ARPKD we investigated the intra- and interfamilial variability in terms of age at diagnosis, administration of antihypertensive therapy, liver involvement and renal function [26]. According to the subclassification of Blyth and Ockenden [5], who defined different grades of severity, 12 patients were assigned to the perinatal, nine to the neonatal, 13 to the infantile and eight to the juvenile subtype of ARPKD. In 11/20 families different subtypes among affected siblings were observed. In seven families affected sibs belonged to adjacent subtypes, while major interfamilial differences were observed in only four families.

The defined subtypes therefore cannot be regarded as appropriate in distinguishing genetic groups of ARPKD. In respect to the severity of ARPKD, there is a wide spectrum of phenotypic manifestations ranging from stillbirths to mildly affected adults, while in contrast interfamilial variability of the clinical picture is generally small. Multiple allelism has to be considered as the most likely genetic explanation. Age of death, however, showed gross variation in eight sibships.

Fig. 1. Ideogram of human chromosome 6p, with an expanded genetic map of the analysed region including the position of ARPKD. Distances are those published by Volz et al. [35].
Genetics

Marquardt [27] was the first to postulate that ‘in surviving individuals, cystic kidneys are inherited dominantly. In non-viable individuals cystic kidneys are recessive.’ The extended classification of Blyth and Ockenden [5] requires genetic interpretation. The authors postulate that ‘lastly, families reported in the literature in which more than one child appears to be affected by the childhood type of disease, should provide evidence for or against the suggested subdivision into four groups’. The authors’ interpretation that these groups represent different single gene determined entities is only valid if there is no overlap between groups within any given family—in other series as well as their own. In the authors’ opinion ‘it therefore seems reasonable to propose that children with childhood type of polycystic disease can be divided into four groups on clinical and pathological grounds, and that a different mutant gene is responsible in each group. These genes could perhaps be allelic, but there is no information on this.’ However, a thorough review of the cases reported by Blyth and Ockenden [5] makes such a rigid classification doubtful. Multiple allelism with only a few different alleles is likely to account for the great variability of manifestation in different families particularly with regard to a possible compound heterozygosity. In addition, this would explain the relatively high intrafamilial concordance in manifestation as well.

Mapping the ARPKD gene to chromosome 6p

In the last 7 years we have collected information about ARPKD families and performed linkage studies. We have excluded linkage with markers on both ADPKD loci: chromosome 16p[28] and chromosome 4q[29]. In the cpk mouse with cystic kidneys the responsible gene has been mapped, but homologous regions in humans are unlikely as possible locations for ARPKD in humans. Linkage has also been excluded with the human homologue of the mouse Tg737 gene [30,31]. After exclusion of several candidate genes such as Na+/K+-ATPases, collagen genes and others, we found linkage with markers on chromosome 6p. We performed linkage analysis in our first study in 16 ARPKD families and localized the ARPKD gene to chromosomal region 6p21-cen with pathologic and evidence for genetic heterogeneity among different clinical phenotypes. Linkage was confirmed by use of adjacent microsatellite markers. The highest lod score of 7.42 was obtained with D6S272 at \(O = 0.00\) [30]. In a more extensive study of severe early onset ARPKD cases (perinatal type) a total lod score of 4.58 (\(O = 0.01\)) was obtained in a collection of 21 American and European families, thus confirming 6p-linkage in severe cases [31]. Figure 1 summarizes the linkage results on the basis of the combined analysis of data [30,31].

Prenatal diagnosis

Increased echogenicity and renal enlargement are the main ultrasonographic signs of ARPKD; oligohydramnios is characteristic but not always present. Repeated sonographic measurements of the kidney length seem to be the most useful parameter. Because of the nearly regular arrangement of nephrons and collecting ducts, disturbances have been postulated to act rather late during embryogenesis. In a certain number of cases enlargement of kidneys is only detected during the second half of pregnancy. This has now been demonstrated in six personally observed cases and many cases reported in the literature [32]. In cases with milder involvement and only a small proportion of dilated nephrons, prenatal diagnosis by ultrasound is even more uncertain. Reports of increased trehalase activity [32] could not be confirmed in cases of ARPKD. After mapping the gene locus for ARPKD to chromosome 6, prenatal prediction by linkage studies is now possible. Our experiences with >20 prenatal diagnoses gave no evidence of genetic heterogeneity [31,33,34].

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