Case Report

Autosomal recessive polycystic kidney disease presenting in adulthood. Molecular diagnosis of the family

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Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is the most common hereditary renal cystic disease in children. The exact incidence is not available and estimates vary widely, ranging from 1:6000 live births in American reports to 1:40 000 in the European literature [1,2]. It is inherited as an autosomal recessive trait and thus it may be seen in siblings but never in the parents.

ARPKD is characterized by bilateral enlargement of kidneys caused by generalized dilatation of the collecting tubules, and is invariably associated with congenital hepatic fibrosis. The majority of cases present at or near the time of birth with severe kidney damage, and almost all of them result in death because of respiratory distress following Potter’s sequence. However, when the diagnosis is made at infancy or later, the patient usually presents severe liver damage and milder kidney involvement [3].

This report documents an ARPKD patient who survived the newborn period and showed as first symptom end-stage renal failure in adulthood without symptomatology related to hepatic fibrosis.

Case report

A 20-year-old man was admitted to our hospital because of biochemical features of advanced renal failure. The patient had been apparently well until 3 months earlier, when he began to experience fatigue, anorexia, weight loss and muscle cramps.

He had presented with palpable masses in both flanks and hepatomegaly at birth. At that time an exploratory laparotomy showed enlarged kidneys with multiple cysts, and a hepatic scintigraphy showed homogeneous hepaticomegaly and splenomegaly. Since then he had not been followed up and his growth and development were apparently normal. There was no family history of renal disease.

On the day of admission temperature was 36.5°C, pulse 90/min and blood pressure was 140/70 mmHg. On physical examination uraemic fetor, cutaneous disease in children. The exact incidence is not available and estimates vary widely, ranging from 1:6000 live apparent features, while the kidneys were not palpable.

Results of laboratory tests included creatinine 16.3 mg/dl, urea nitrogen 110 mg/dl, uric acid 3.8 mg/dl, sodium 140 mEq/l, potassium 4.4 mEq/l, calcium 4.5 mg/dl, phosphorus 6.8 mg/dl, bicarbonate 8.9 mmol/l, total proteins 66 g/l with albumin 41 g/l, total bilirubin 0.7 mg/dl, SGOT 33 i.u./l, SGPT 13 i.u./l, alkaline phosphatase 298 i.u./l, leukocytes 4.9×10⁹/l, haemoglobin 8 g/l, platelets 86×10⁹/l and prothrombin time 96%. Urinary protein were 813 mg/24 h with a normal urine sediment.

Abdominal ultrasound examination showed normal sized kidneys with increased cortical echogenicity, loss of the corticomedullary differentiation, and many bilateral small cysts; no alteration in the urinary tract was seen (Figure 1); hepatosplenomegaly and diffuse parenchymal liver alteration were also present. A liver biopsy specimen was obtained by an ultrasound-guided

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puncture and revealed hepatic fibrosis (Figure 2). Endoscopy excluded oesophageal varices, and the patient refused a portocavography to evaluate portal hypertension. Abdominal ultrasound examination in the parents and two sisters was completely normal.

The diagnosis of ARPKD was made on the basis of kidney and liver affection and the absence of familial history of nephropaty. Haemodialysis was begun.

To reinforce this diagnostic, a linkage analysis of the family using 6p21 markers was performed. The microsatellites used were the following: D6S269, D6S465, D6S427, D6S436, D6S272, D6S466, D6S295, D6S294, D6S257. The PCR products were run in 6% acrylamide gels and developed with the silver staining technique [4]. The results were compatible with linkage to the ARPKD gene with the affected proband, a carrier sister and a non-carrier sister (Figure 3).

Discussion

ARPKD, referred to in the past as infantile polycystic kidney disease or polycystic kidneys Potter type I, has a variable clinical spectrum, but typically patients are identified in utero or at birth, and the clinical course is most often characterized by rapidly fatal outcome because of pulmonary hypoplasia, atelectasis, and respiratory insufficiency [5]. However, for those who survive perinatal period, the chance of being alive at 15 years is considered about 50–80% [6]. In one of the most representative prognostic analyses reported, 55 ARPKD patients were retrospectively reviewed; 23 patients (42%) presented within the first month of life, and 12 of them (about 50%) survived beyond 2 years of age; for this selected study group survival rates revealed that 79% were alive at 1 year, 51% at 10 years and even 46% at 15 years [7]. In perinatal period survivors, glomerular filtration rate can either stabilize or even improve over the first months, but it decreases after the first year and progresses variably to end-stage renal failure [7]. In a retrospective study that included 14 patients in whom the diagnosis of ARPKD was made before 2 weeks of life, nine children were still alive at the time of the report: five of them remained with normal serum creatinine (aged between 8 months and 7 years), while four presented renal insufficiency (aged between 7 and 14 years), and one began haemodialysis at 4 years of age [8].

Therefore our case illustrates one of these infrequent patients presenting with ARPKD at birth who survive the perinatal period and remain asymptomatic until adulthood. The diagnosis was made early on the basis of both exploratory data and surgically findings, combined with absence of family history of kidney disease (polycystic kidney disease is sometimes seen in seemingly sporadic cases that may represent new mutations of autosomal dominant polycystic kidney disease, but in this patients features of ARPKD are absent); nevertheless, he did not present pulmonary manifestations. Kidneys were increased in size at birth, although serum creatinine was unknown to us. He was in good condition until uraemic symptoms developed at 20 years, when data resulting from laboratory, ultrasound and liver biopsy pointed the diagnosis of ARPKD. Linkage analysis provided further consistent data, disclosing also that one sister could be a carrier of the disease. Moreover, the patient had blood pressure in the normal range, while in majority of ARPKD patients hypertension is already present at diagnosis or later in the clinical course, and is the most significant cause of morbidity and mortality among perinatal survivors [7].

Another atypical trait in our case is liver involvement. Liver pathological findings confirmed hepatic fibrosis and the patient had splenomegaly and hypersplenism, probably on account of portal hypertension. But there was no clinical manifestations subsequently related. Usually, the severity of portal hypertension in ARPKD ranges from minimal in infants to marked in older patients, and in the latter group clinical presentation is dominated by signs of portal hypertension, mainly gastrointestinal bleeding related to oesophageal varices [3]. Although some reports suggest the possibility of adulthood presentation without severe liver involvement [2,9], we have only found four cases reported to date in the literature; the first is a girl that presented with end-stage renal failure requiring haemodialysis and mild liver affection at 14 years of age [10]; the second belongs to a follow-up of ARPKD siblings, and the patient is also a 14-years-old girl diagnosed at birth who by that age had no clinical signs of liver involvement while she presented advanced renal failure [8]; the other cases are two siblings presented with renal failure and asymptomatic hepatic fibrosis at 14 and 18 years of age respectively [11]. Although these cases seem to be extremely unrequent, we believe that they may be underdiagnosed as the sonography of ARPKD diagnosed in adulthood is not very specific; thus the suspicion of ARPKD must be raised when portal hypertension is present in a young adult with end-stage renal failure. Finally, it should be remembered that hepatic fibrosis can also occur in autosomal dom-

Fig. 2. Liver biopsy showing hepatic fibrosis.
Autosomal recessive polycystic kidney disease presenting in adulthood

Fig. 3. Pedigree of the kindred. Open symbols, unaffected; solid symbols, affected; squares, men; circles, females. Haplotypes from the 6p21 (ARPKD) region are below each symbol; microsatellite alleles: A, D6S269; B, D6S465; C, D6S427; D, D6S436; E, D6S272; F, D6S466; G, D6S295; H, D6S294; I, D6S257. The chromosomes carrying the mutated gene are represented in bold. The offspring show the three possibilities: affected, carrier, and non-carrier.

In conclusion, great differences are observed in clinical manifestations of ARPKD. Although the diagnosis is not difficult in the majority of cases presenting at birth, we believe that ARPKD may be underdiagnosed in adulthood because the sonographic data are not specific. Moreover, a correlation between age and hepatic involvement is not always seen, so this disease must be suspected when portal hypertension is present in a young adult with renal failure. Nowadays, linkage analysis helps in establishing the diagnosis and it is essential in prenatal diagnosis.

References

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Iniant polycystic kidney disease, but this is a rare and clinically mostly asymptomatic finding [12]. Ultrasound data at the time of diagnosis in a newborn with ARPKD almost always show nephromegaly with increased cortical echogenicity, loss of corticomedullary differentiation and multiple small cysts. But the sonographic characteristics of the kidney change with long-term survival, presenting a loss of uniformity because kidney size does not continue to increase; rather a decrease in size with increased echogenicity occurs because of progressive fibrosis, making the diagnosis more difficult [13]. Moreover, prenatal diagnosis cannot always be provided only by ultrasound, because typical ultrasonographic features of ARPKD in a fetus are often seen for the first time in the third trimester of gestation [14].

In 1994 linkage analysis was performed in 16 ARPKD families and localized the ARPKD gene to the chromosomal region 6p21-cen [15]. After that, linkage was confirmed in 22 families with the severe phenotype, suggesting that, despite the wide variability in clinical phenotypes (even between siblings), there is a single gene causing the disease [16]. These data have important implications for prenatal diagnosis, allowing the diagnosis in the first trimester of pregnancy in those families who have already had an affected child. Up to now the ARPKD gene has not been identified. Thus the molecular diagnosis is based in linkage analysis performed with several microsatellites which are localized around the gene, and it can help in the diagnosis in sufficiently large families.

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