DESCRIPTION OF THE NEPHROLOGY TRAINING PROGRAM AT THE UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

Since its inception 20 years ago, the Fellowship Program of the Division of Renal Diseases and Hypertension at the University of Colorado School of Medicine has trained 115 fellows under the auspices of a National Institutes of Health Training Grant. Approximately 50% of these fellows now hold faculty positions at various medical schools in the United States. The program is characterized by a balance between emphasis on excellence in clinical teaching and the provision of research opportunities. Clinical services are overseen by 16 faculty members at University Hospital, Veterans Administration Hospital, and Denver General Hospital. In addition to an active consulting service, the fellows are involved in the care of a sizeable dialysis population both on hemodialysis and home peritoneal dialysis. An acute dialysis facility in a tertiary-care hospital is actively involved in the care of patients in intensive care units. The renal transplantation service works in close and harmonious association with the Department of Surgery. The medical care of these patients is entirely under the supervision and direction of members of the renal division. Since its reorganization 4 years ago, more than 100 patients are monitored by the renal fellows and faculty in the transplantation clinic. After their clinical training, for the ensuing 2 years, the fellows have a broad range of laboratories from which to choose for their research experience. There are laboratories actively engaged in the study of renal physiology, biochemistry, cellular biology, and molecular biology directed primarily to the understanding of hormone action in the kidney, various aspects of acute and chronic renal failure, and the pathophysiology of hypertension. In addition, there are opportunities for clinical research in volume regulation, diabetic nephropathy, and polycystic kidney disease. The educational activities of the division are centered around a daily meeting including a basic science course, research conferences, journal clubs, and clinically oriented conferences, all with high fellow and faculty involvement. The University of Colorado School of Medicine offers a broad, balanced program primarily directed at the training of individuals to pursue academic careers but also emphasizing excellence in clinical pursuits.

Autosomal Recessive Polycystic Kidney Disease: Issues Regarding the Variability of Clinical Presentation[1]

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F.M. is a 29-yr-old female with a history of cystic kidney disease of unclear etiology who presented with intermittent right upper quadrant pain. She was not taking medication and did not use alcohol or drugs. Her past medical history was unremarkable, without history of gastrointestinal bleeding, gallbladder disease, or hepatitis. She reported no unusual environmental exposures. Her blood pressures were 110/60 mm Hg at age 19 and 110/80 mm Hg at age 22. Her family history was unremarkable for kidney or liver disease, although renal imaging studies had not been performed on her relatives.

Her physical examination demonstrated a blood pressure of 100/70 mm Hg and a pulse rate of 80 beats per minute. Her liver span was 12 cm, and her kidneys were not enlarged. The remainder of her physical examination was completely normal.

A review of her laboratory data was significant for a serum creatinine concentration of 1.9 mg/dL at 19

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yr, 2.3 mg/dL at 22 yr, and 3.2 mg/dL at 29 yr of age. Her liver function tests and electrolytes were normal. Urinalysis was unremarkable, and 24-h urinary protein excretion was 29 mg/day. Her renal ultrasound demonstrated left and right kidneys measuring 9.3 and 9.0 cm in length, respectively. No cysts were seen, and differentiation of the cortex and medulla could not be made.

Computed tomography without contrast of the abdomen showed polycystic kidneys, with diffusely distributed cysts and probable hepatic fibrosis. Abdominal angiography revealed splenic varices with shunting of blood from the liver to the spleen, consistent with hepatic fibrosis. The diagnosis of autosomal recessive polycystic kidney disease (ARPKD) was then made.

INTRODUCTION

ARPKD is an inherited cystic kidney disorder. Estimates of the frequency of occurrence of ARPKD vary from 1:10,000 to 1:40,000 (1). This variability is the result of the different populations and methodologies used in the studies. Patients usually present with renal insufficiency *in utero* or infancy, but ARPKD can have a delayed clinical presentation. The case presented here, with renal cysts and hepatic fibrosis, is typical for ARPKD presenting clinically in a young adult, as compared with the primarily renal presentation seen *in utero* and in infancy (2).

Family history and radiographic findings are usually adequate to arrive at a diagnosis. Family history classically shows disease in 25% of siblings and no disease in the parents. Radiographic studies in adults show small renal cysts and hepatic fibrosis. The prognostic differences among the various polycystic kidney diseases makes establishing a diagnosis important.

RENAL PATHOLOGY

ARPKD is a bilateral disease. The kidneys have a normal shape, even with fetal lobulations. Kidney size varies inversely with the age of diagnosis, with patients who present *in utero* or at birth having massively enlarged kidneys, renal failure, and oligohydramnios. Patients without clinical or laboratory abnormalities until late childhood have average-size or slightly enlarged kidneys that gradually increase in size as the patient ages. The finding of small kidneys in our patient is likely the result of damage associated with chronic renal failure, which overwhelms any increase in size associated with the cysts.

Opalescent dots less than 2 mm in size stud the surface of spongy kidneys, representing cystic dilation of the collecting systems (3). Slices through the kidney show fusiform cystic dilations that run radially through the cortex and medulla. Demarcation of the cortex and medulla can be made out, despite the presence of cysts. The renal pelves are appropriately enlarged for the size of the kidneys, and the pelves and ureters are normal in shape.

Microdissection reveals primarily saccular as well as fusiform dilations of the papillary collecting ducts. Occasionally, the distal convoluted tubules and the ascending limbs of the loops of Henle are involved. The last generation of tubules formed embryologically are the cortical rays and are predominantly affected, being dilated through their entire length (4). The cysts are sometimes noted to branch, consistent with a collecting duct origin. The cysts are connected to normal-appearing tubules and glomeruli. Glomerular cysts are not usually seen; however, they have been observed in ARPKD (4). Decreased numbers of histologically normal glomeruli and tubules are crowded together between the cysts. Presenting newborns can have 80% of tubules involved. The level of tubular involvement has been reported to correspond with mortality in some pathologic studies (5). Patients presenting during adulthood usually have less renal involvement (10% of tubules). Interstitial, renovascular, and glomerular disease are not major features of ARPKD.

Microscopic examination of the cyst walls demonstrates increased numbers of cuboidal or low columnar epithelial cells. The mechanism of cyst formation has not been established; however, some workers suggest that disordered growth regulation leading to epithelial cell hyperplasia is responsible for cyst formation (3). The epithelial cells and basement membrane are of normal dimensions in the cystic tubules but increased in number, supporting the hypothesis of hyperplasia (5). Obstruction leading to increased intraluminal pressure, tubular stretching, and cyst formation, as well as the possibility of abnormal basement membrane compliance leading to tubular stretching and cyst formation, has also been proposed to be related to the pathogenesis of this disorder, although supportive studies are lacking (6).

Whether a crucial time exists during embryologic development for cyst development or whether it is related to the severity of the disease is unclear, but the microdissection studies of Osathanondh and Potter demonstrate that the earlier-forming collecting tubules are more affected than the later-forming proximal collecting tubules (4). Therefore, hyperplastic changes occur after the induction of the metanephric blastoma and after the attachment of the nephrons to the ureteral bud, both of which take place in the fifth week of gestation.

EXTRARENAL PATHOLOGY

ARPKD is always associated with some degree of congenital hepatic fibrosis (CHF). In CHF, there is an

increase in fibrous connective tissue in the portal tracts and an increase in bile duct number. The bile ducts are mildly dilated and form rings of interconnecting sacs in the portal zones instead of separate tubules (7).

The etiology of CHF has been proposed to be the result of an overgrowth of biliary epithelium and its supporting connective tissue. This overgrowth leads to bile duct dilation and improper formation of the ductal plates, leaving a network of small bile ducts surrounding the portal vein (7). The appearance of the dilated bile ducts in ARPKD is regarded as an arrest of normal cell differentiation. The bile duct abnormalities appear to occur embryologically at a specific level of the duct system. This level corresponds developmentally to the 12th to 20th generations of branching of the biliary epithelial bud (6). The remainder of the other hepatic cells are structurally normal.

When the age of clinical presentation increases to childhood or early adulthood, the level of renal involvement appears to be more similar to autosomal dominant polycystic kidney disease (ADPKD) and the level of CHF greater than when a diagnosis is made *in utero* or in infancy (2). Then, both renal and hepatic involvement gradually increase with age. Extrarenal cysts in ARPKD are rare but have been reported in both the pancreas and liver (3). Berry aneurysms have also been reported in patients with ARPKD (3). The rarity of these extrarenal findings suggests that these may be coincidental findings in ARPKD.

GENETICS

Most investigators believe that ARPKD is a single entity with a broad range of clinical and pathologic presentations (1–3,6,8,9). However, Helczynski and coworkers argue that there are two distinct diseases, one being infantile polycystic disease (IPCD) and the other being CHF with renal tubular ectasia (10). IPCD was defined as a disorder with a clinical presentation of renal failure before the age of 6 months, with no apparent clinical liver disease. Patients with CHF with renal tubular ectasia presented between 6 months and 6 yr of age with portal hypertension caused by hepatic fibrosis. In patients with CHF with renal tubular ectasia, slowly progressive renal failure was apparent after the presentation of liver abnormalities. Tissue specimens were examined in all cases. Five patients age 3 to 19 yr with IPCD and five patients age 6 months to 14 yr with CHF were studied. Patients with predominant CHF demonstrated centrally located renal collecting tubule cysts with small cysts growing over time, and the liver had predominantly interlobular duct involvement. In IPCD, the collecting tubule cysts were more peripherally located than in CHF, with cysts remaining the same size with time, and the liver had smaller bile duct involvement. That study may demonstrate two distinct disease processes; however, more likely these are phenotypic differences within the entity of ARPKD when different ages of presentation are considered.

Kaplan *et al.*, in 1988, suggested that the heterogeneity of ARPKD is due to variable phenotypic expression of the same gene defect and not to multiple disease processes placed under one name (8). They described two siblings from a family with no history of renal disease. One brother died a few hours after birth from pulmonary atelectasis secondary to oligohydramnios. Autopsy revealed large cystic kidneys and evidence of hepatic fibrosis. His asymptomatic sister was screened at age 16; bilateral cystic kidneys were demonstrated by ultrasound, and hepatic fibrosis was found by liver biopsy. The conclusion was that this most likely represented ARPKD with variable phenotypic expression.

CLINICAL PRESENTATION

When ARPKD presents at birth, we find large abdominal masses representing the kidneys. Renal function is poor, resulting in oliguric renal failure and hypertension. The low urine output *in utero* causes oligohydramnios, resulting in poorly developed lungs that often cause death and Potter facies, consisting of deep-set eyes, flat-beaked nose, micrognathia, low-set ears, and extremity contractures. Clinically significant liver involvement is rare; however, microscopic liver involvement is usually present (11).

Presentation in childhood or adult life is often due to symptoms related to CHF such as portal hypertension, hepatomegaly, and cholangitis. Liver function studies tend to be normal. Patients may present with renal manifestations such as asymptomatic elevated creatinine levels, hypertension, hematuria, and mild proteinuria. Patients presenting in childhood often progress to renal failure over years.

DIFFERENTIAL DIAGNOSIS

ARPKD and ADPKD are two conditions that exhibit similar characteristics when diagnosed both *in utero* and in childhood, with diagnostic differentiation being difficult. There are characteristics of ARPKD and ADPKD that can help to differentiate the two disorders. A number of renal cystic diseases may also appear similar to ARPKD (1,3,12). These other cystic diseases usually are easily differentiated, even in the presence of CHF, because they are accompanied by a variety of physical abnormalities to constitute a syndrome (Table 1).

TABLE 1. Differential diagnosis of ARPKD

Disease (3, 12)	Differentiating Features
Glomerulocystic Kidney Disease	Not inherited; >50% of glomeruli have dilation of Bowman's space; liver spared.
Simple and Acquired Cysts	Not inherited; associated with primary hyperaldosteronism, chronic hypokalemia, and chronic urinary tract infections; no liver involvement.
Medullary Sponge Kidney	Usually not inherited (rarely dominant); cortex spared; normal renal function; no liver involvement.
Nephrophthisis Complex	Small kidneys; medullary cysts only; interstitial renal fibrosis; occasional liver involvement; recessive and dominant inheritance have been observed.
Tuberous Sclerosis	Dominantly inherited; extrarenal hamartomas.
Diffuse Cystic Dysplasia	Not inherited; unilateral; liver not involved.
ADPKD	Dominant inheritance; rare hepatic fibrosis; liver cysts in 40–70% of cases.
Ivemark's Syndrome	Renal-hepatic-pancreatic dysplasia; sporadic inheritance; hepatic fibrosis.
Trisomy 13	Sporadic inheritance; multiple physical deformities; rare hepatic fibrosis.
Beckwith-Wiedemann Syndrome	Exomphalos; macroglossia; gigantism; hepatomegaly; possibly autosomal dominant.
Meckel-Gruber Syndrome	Occipital encephalocele; polycystic kidneys; polydactyly; occasional hepatic fibrosis; autosomal recessive.
Zellweger Syndrome	Cerebrohepatorenal syndrome; autosomal recessive.
Jeune's Syndrome	Thoracic dystrophy; short-limbed dwarfism; rare hepatic fibrosis; autosomal recessive.
Bardet-Beidl Syndrome	Retinal dystrophy; polydactyly; mental retardation; mild obesity; rare hepatic fibrosis; autosomal recessive.

ADPKD can present *in utero* or in childhood, although more commonly in adult life. Extrarenal cysts can develop in other organs such as the liver; however, this is rare in childhood (1). Chronic renal insufficiency can also develop in childhood, and hypertension commonly occurs before the loss of renal function. Thus, in infants without a complete family history, it can be hard to differentiate the two diseases.

Kaariainen and coworkers, in a retrospective study using death certifications and medical records from 1974 to 1983, analyzed 93 ARPKD and ADPKD children under the age of 16 whose diagnosis was confirmed by at least one imaging study (9,11,13). ADPKD patients required an affected parent or grandparent for diagnosis, whereas ARPKD patients had a negative family history for cystic renal disease except for affected siblings. The renal cysts in the ADPKD children were larger than 1 cm in 12 of 13 patients when measured by ultrasound or computed tomography, whereas renal cysts were smaller than 1 cm in two of two ARPKD children imaged by ultrasound and computed tomography. Kidneys were less echogenic than the liver by ultrasound in all ADPKD children, whereas both ARPKD children had more echogenic kidneys than livers. Renal collecting systems assessed by intravenous pyelogram were normal in all ADPKD children, whereas the collecting systems were enlarged in all ARPKD children studied. Periportal fibrosis was present in 1 of 12 ADPKD and both ARPKD children.

With this information, Kaariainen *et al.* then looked at patients without a clearly documented family history and found that 14 of 16 could be classified by information from imaging studies alone (13).

DIAGNOSIS

Ultrasound, biopsy, and family history are usually sufficient to make the diagnosis of ARPKD. Recessive inheritance, small cysts, and CHF are the hallmarks of ARPKD. Ultrasonography of siblings and parents is important because many people have subclinical, previously unrecognized disease. A negative family history does not differentiate between ARPKD and ADPKD, because a negative family history is found in up to 25% of newly presenting ADPKD cases. In most cases, ADPKD will be distinguishable from ARPKD by use of the above studies.

Prenatal diagnosis can be accomplished by ultrasound in some patients with ARPKD and ADPKD (2, 14–17). Bilaterally enlarged echogenic kidneys have

been reported in both ADPKD and ARPKD fetuses (2). Cysts are rarely seen *in utero* in ARPKD or ADPKD patients by ultrasonography. Renal abnormalities have been seen as early as 17 wk of gestation in ARPKD (2) and 16 wk in ADPKD (15). Unfortunately, a negative ultrasound cannot rule out ARPKD or ADPKD.

ADPKD can be distinguished from ARPKD *in utero* by differences in family history. If parents are unaffected and young, grandparents should be screened to rule out ADPKD. Renal ultrasonographic abnormalities have been reported in a study of eight affected fetuses from ADPKD families, demonstrating two with renal cysts, five with enlarged echogenic kidneys, and one with a normal examination (15). No antenatal liver involvement could be detected by ultrasound in the fetuses with ADPKD but have been reported *in utero* in ARPKD (2,15). Renal cysts have also been reported *in utero* in ARPKD (18).

PROGNOSIS

The prognosis of a patient with ARPKD is difficult to assess, given the low incidence rate of the disorder and the variability in presentation.

The data of Kaariainen *et al.* from Finland finds that only 19% of children with ARPKD survive infancy (11). Most deaths are in the first month of life and are due to pulmonary atelectasis and respiratory failure from oligohydramnios. Of the 18 children who survived the first month of life, only 4 (22%) died during long-term follow-up.

Cole et al. retrospectively examined the medical charts of 17 patients diagnosed before 1 yr of age with ARPKD who were alive more than 1 month after birth (18). After an average of 6 yr of follow-up, two were dead, five were in renal failure, and eight were doing well, but only one had a normal GFR as estimated from serum creatinine concentration. This suggests that ARPKD is not a uniformly fatal disorder.

The progression of CHF has not been longitudinally studied. Patients have been reported with biliary stasis and splenic and esophageal varices (1,11). Hepatic failure has not been reported.

CONCLUSION

ARPKD is a rare disease with a broad spectrum of presentations. Infants presenting clinically with ARPKD have enlarged cystic kidneys and some degree of renal failure. Older children and adults present with hepatic disease from CHF and tend to have less-severe cystic renal involvement than do infants. The renal and hepatic lesions progress slowly over time, as is demonstrated by our patient. ARPKD can usually be distinguished from ADPKD by its association with hepatic fibrosis. These patients are managed with supportive care.

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