

Clinical manifestations of hereditary cystic kidney disease

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1. ABSTRACT

Genetic mutations of discrete loci are the cause of a diverse array of polycystic kidney disease syndromes which present in distinct, as well as overlapping, phenotypic and hereditary patterns. Since molecular diagnostics are not currently a feasible clinical tool for the diagnosis of most cystic kidney diseases, physicians must rely upon their clinical acumen and knowledge base in order to identify these patients. The goal of this manuscript is to review the hereditary patterns, basic epidemiology, and phenotypic features of the most common of the cystic renal diseases so as to increase the awareness of these renal diseases among practicing physicians. Specifically, the genetic and phenotypic features of autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, nephronophthisis-medullary cystic kidney disease complex, Bardet-Biedl syndrome, and oral-facial-digital syndrome 1 will be reviewed.

2. INTRODUCTION

Hereditary polycystic kidney disease represents a diverse spectrum of renal diseases with distinct patterns of inheritance, phenotypic expression and pathophysiology. Cyst development and its attendant complications, including renal insufficiency, may be the primary ailment garnering medical attention or a minor part of genetic syndrome. Our focus is to review the clinical spectrum of hereditary cystic kidney diseases so that clinicians are able to identify these patients early and treat them proactively. We will review autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive PKD (ARPKD), nephronophthisis (NPHP)-medullary cystic kidney disease (MCKD) complex, Bardet-Biedl syndrome (BBS), orofacial digital syndrome (OFD), tuberous sclerosis, and von Hippel-Lindau disease with an eye towards the genetics of inheritance and their clinical manifestations.

3. AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

3.1. Genetics

Eighty five percent of ADPKD cases are caused by mutations of the *PKD1* locus located on human chromosome 16p13.3 while mutations of *PKD2*, located on chromosome 4q21, are responsible for the remaining 15% of human cases (1,2). *PKD1* related ADPKD is characterized by a relatively aggressive renal phenotype with renal failure by an average age of 54.3 years old while renal failure due to mutations of *PKD2* occur 20 years later, at an average age of 74 years old (3). Though commonly found as heterozygous mutations at either *PKD1* or *PKD2* locus, murine models and human probands have been described which are trans-heterozygotes (single mutated allele at each locus) and they present with a more aggressive renal disease than either single mutant allele alone (4,5). Homozygous mutations at either locus alone have not been described in humans, presumably reflecting a lethal condition that has been experimentally reproduced in mice (6).

Many investigators have sought to correlate genotypic changes with phenotypic manifestations in order to develop insight into the importance of each domain within the polycystin-1 (PC-1) and polycystin-2 (PC-2) proteins encoded by *PKD1* and *PKD2*, respectively. However, no mutation “hot spot” has been identified within the *PKD1* and *PKD2* loci. Instead, investigators have discovered 298 *PKD1* and 106 *PKD2* unique mutations and these are assembled in the ADPKD Mutation Database maintained at the Mayo Clinic (<http://pkdb.mayo.edu>) (7). Although no clear genotype-phenotype correlations have been uncovered, some general associations between the location of mutations and their phenotypic expression have been found. Mutations at the 5' end (amino terminus) of *PKD1* are closely linked to vascular complications and early renal failure compared to 3' (carboxy terminus) mutations. However, the specific type of mutation (missense, frameshift etc) is not associated with particular phenotypic features (8,9). Even with these genotype and phenotype associations, significant intrafamilial phenotypic variability is observed and points to the role of other genetic or environmental factors influencing progression of disease (8-10). For example, dizygotic ADPKD twins develop end stage renal disease (ESRD) at an average of 6.9 years apart from each other while monozygotic twins develop ESRD 2.1 years apart from each other suggesting a role for environmental and genetic factors in renal disease progression (11). Gender also appears to influence renal disease progression as females tend to have lower rates of progression to ESRD than males (12,13).

Renal cyst development is hypothesized to be related to the acquisition of secondary somatic mutations in the wildtype *PKD1* or *PKD2* allele in the “two hit model” of ADPKD, producing clonal expansion and “growth advantage” over the remaining renal tubular epithelia (14-16). Genetic analysis of ADPKD cysts demonstrate that they are monoclonally derived due to a loss of heterozygosity (14). Cyst development occurs in only a minority of tubules (<5%), yet this subset of susceptible tubules is able to induce progressive renal failure (15,17). The mechanism by which this second “hit” occurs to the normal allele is not known, but contributes to the phenotypic variability observed in ADPKD.

3.2. Clinical Manifestations

3.2.1. Epidemiology

ADPKD is the most common genetic renal disease in the world with a prevalence of 1:400 in the United States (US), but with estimates throughout the world that vary from 1:1,111 in France to 1:4,033 in Japan (18-20). It is a cause of renal failure in approximately 4.4% of all ESRD patients and accounts for ~2.2-2.4% of incident ESRD patients in the US (21).

3.2.2. Renal Manifestations

Renal cyst development and growth is the primary manifestation of ADPKD and this leads to complications including hypertension, urinary concentrating abnormalities, pain (due to cyst hemorrhage, infection, nephrolithiasis, cancer) and renal failure. See Table 1 for diagnostic criteria for ADPKD.

Clinical manifestations of hereditary cystic kidney disease

Table 1. Clinical Criteria for the diagnosis of cystic kidney disease

Cystic Disease	Renal	Gene Affected	Inheritance	Diagnostic Criteria
ADPKD		PKD1, PKD2	Autosomal Dominant	In pt with positive family history (50% risk) (Ref. 218,219):
				Renal sonogram
				Age 15-29 2 cysts (uni- or bi-lateral)
				Age 30-59 \geq 2 cysts in each kidney
				Age >60 \geq 4 cysts in each kidney
				In pt without family history (unknown risk) (Ref. 220)
				Exclude unusual clinical features (characteristics seen with other PKD syndrome)
				+ cysts with <i>small</i> kidneys->acquired cystic disease
ARPKD		PKHD1	Autosomal Recessive	+ cysts with <i>large</i> kidneys->consider ADPKD; look for other classic features (hepatic cysts, mitral valve prolapse, etc) and consider molecular testing
				a) Exclude cystic disease in parents (dominant inheritance)
				b) Renal sonogram with enlarged echogenic kidneys (>95 th percentile), with or without small (<2 cm) cysts
NPHP		NPHP1-6,AHI1	Autosomal Recessive	c) if above equivocal, abdominal sonogram to look for biliary dysgenesis and/or portal hypertension
				a) Exclude cystic disease in parents (dominant inheritance)
				b) Renal sonogram with normal to small echogenic kidneys with or without cortico-medullary or medullary cysts
				c) Extra-renal manifestations-retinal, neurologic, hepatic, and skeletal
				d) Progression to ESRD by 30 years of age
MCKD		MCKD1, 2	Autosomal Dominant	e) Kidney biopsy for classic findings
				a) Parents with history of cystic kidney disease
				b) Renal sonogram with normal to small echogenic kidneys with or without cortico-medullary or medullary cysts
				c) Progression to ESRD after 30 years old
BBS		BBS1, 2, 3 (ARL6), 4, 5, 6 (MKKS), 7, 8 (TTC8), 9 (B1), 10, 11 (TRIM32), 12	Autosomal Recessive (triallelic inheritance)	d) Hyperuricemia and/or gout
				Diagnosis: 4 or more primary features OR 3 primary and 2 secondary features
				<i>Primary features</i> (Ref. 176) Rod-cone dystrophy, Polydactyly, Obesity, Learning disability, Hypogonadism in males, Renal abnormalities
OFD type -1		OFD1	X-linked dominant	<i>Secondary features</i> (Ref. 176) Speech disorder/delay; Strabismus/cataracts/astigmatism; Brachydactyly (short)/syndactyly (webbed fingers); Developmental delay Polyuria/polydipsia (nephrogenic diabetes insipidus); Ataxia/poor coordination/imbalance; Mild spasticity (esp lower limbs); Diabetes mellitus; Dental crowding/hypodontia/small roots/high arched palate; Left ventricular hypertrophy/congenital heart disease; Hepatic fibrosis
				Female Gender (lethality in males)
				Oral: Cleft palate, lingual hamartomas, cleft or pseudocleft of lip, bifid or lobulated tongue, hyperplastic and supernumerary buccal frenulae, hypodontia
				Facial: facial asymmetry, hypertelorism, broad nasal bridge, hypoplasia of nasal alae
				Digital: brachydactyly, clinodactyly, syndactyly
				Neurologic: Mental retardation, agenesis of corpus collosum, arachnoid cysts, porencephaly, hydrocephalus
				Renal: Polycystic kidneys of normal size, small cysts (<1 cm), normal reniform shape, histopathology demonstrates glomerular cysts

3.2.2.1. Hypertension

Hypertension is a common early complication of ADPKD often affecting individuals without evidence of renal dysfunction, hematuria or proteinuria (22). Because vascular and cardiovascular diseases are common causes for morbidity and mortality, investigators strongly advocate for early treatment of hypertension (23). However, there is controversy regarding the optimal blood pressure (BP) goal and whether inhibitors of the renin-angiotensin system have a specific benefit in ADPKD.

The Modification of Diet in Renal Disease (MDRD) study randomized ADPKD patients with glomerular filtration rates (GFRs) of 13-24 ml/min/1.73m² to two blood pressure goals; (a) a low BP group where the

goal was a mean arterial pressure (MAP) <92 mm Hg or (b) a standard BP group where the goal was a MAP<107 mm Hg. Patients assigned to the lower BP goal developed a faster decline in renal function than the standard MAP group (24). In a separate arm of the study, patients with GFRs of 25-55 ml/min/1.73m² were similarly randomized to low or standard BP goals, but no difference was seen in the rate of decline in GFR during 2.2 years of intervention and follow up (24). Long term follow up, which occurred ~7 years after completion of the MDRD study, indicated that ADPKD patients with GFRs of 25-55 ml/min/1.73m² randomized to the lower BP target reduced their risk for ESRD (25). Another study randomized 75 ADPKD patients with left ventricular hypertrophy (LVH) to a BP target of <120/80 mm Hg or <135-140/85-90 mm Hg, and

then measured the left ventricular mass index (LVMI) and renal function over a period of seven years (26). The decline in renal function was similar between both groups, but LVMI decreased 35% in the lower BP group, but only 21% in the higher BP group (26). Though no study has adequately addressed the question of the optimal BP goal in ADPKD, most experts believe that controlling BP < 130/80 mm Hg as a reasonable goal until studies are designed to answer the question definitively (27).

Inhibition of the renin-angiotensin system (RAS) with angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) is also controversial, but several lines of evidence suggest that these anti-hypertensives may prove beneficial in ADPKD. It is hypothesized that cyst development induces local renal ischemia which activates the RAS (28), whether this translates to systemic activation of the RAS remains controversial (29-31). On the other hand, local, tissue based activation of the RAS has been demonstrated in kidney. Specifically, there is (a) ectopic synthesis of renin from cysts and dilated tubules (32,33), (b) synthesis of chymase-like enzymes that generates local angiotensin II (34), and (c) reduction of renovascular resistance, augmentation of renal blood flow and filtration fraction after administration of ACEi (31,35).

Disruption of the RAS slows the decline in renal function and proteinuria in some human ADPKD studies while others have not shown a difference (36-38). A meta-analysis of eight studies which included 142 ADPKD patients demonstrated that ACEis reduced proteinuria and the decline in renal function in individuals with greater baseline levels of urinary protein excretion (39). Although there is no conclusive evidence to support the use of ACEis or ARBs in ADPKD, the fact that ACEi/ARBs (a) are relatively safe medications with a long history of use in other nephropathies, (b) reduce proteinuria, a marker of progressive kidney disease, and (c) are able to potentially reduce intra-renal activation of RAS, suggests that ACEis and ARBs should be used in ADPKD along with other anti-hypertensives to achieve BP < 130/80 mm Hg. To better evaluate the efficacy of ACEis and ARBs in ADPKD, a NIH sponsored randomized placebo controlled clinical trial is underway (HALT PKD).

3.2.2.2. Urinary concentrating ability

An inability to maximally concentrate urine is an early manifestation of ADPKD and commonly occurs long before the development of renal insufficiency (40-42). This defect has been described by different groups and is believed to be related to distortion of the medullary architecture (42) and mislocalization or altered expression of aquaporins; however, the latter defect is controversial (43-46). Children with impaired urinary concentrating ability are at greater risk for hypertension (47). In a retrospective analysis of the MDRD, ADPKD patients with the most dilute urine lost GFR at a greater rate per year than individuals with a more concentrated urine (48). In addition individuals that excreted greater volumes of urine (>2.85 L/day) developed the greatest decline in GFR and also exhibited the highest MAP (48). These defects in

water metabolism, blood pressure and decline in renal function in PKD did not take on much clinical significance until it was demonstrated that (a) vasopressin type 2 receptor expression was upregulated in PKD and that (b) antagonism of this receptor reduced cyst development (44,49). It has since been proposed that disordered water metabolism is the primary event leading to elevations in vasopressin which in turn induce systemic hypertension through peripheral vasopressin receptors and upregulation of intra-renal Na absorption, and activation of renal vasopressin receptors that induce cyst growth (46).

3.2.2.3. Cystic complications

Renal pain can be caused by cyst hemorrhage, cyst infection, nephrolithiasis and, less commonly, renal cancers. An awareness of these complications coupled with accurate diagnosis and early treatment will help to reduce morbidity and mortality associated with these disorders.

Cyst hemorrhage classically presents with acute flank or abdominal pain and gross hematuria without fever. However, hematuria is not a consistent finding since cysts may be walled off from the nephron from which they were derived, and, thus, do not have access to the urinary tract. Nonetheless, gross and microscopic hematuria are common findings in ADPKD; though this may not necessarily reflect hemorrhage, cyst hemorrhage is commonly inferred (50). Kidney size positively and renal function negatively correlate with the number episodes of hematuria suggesting a relationship between cyst size and the risk of hematuria, or cyst hemorrhage (50).

Identification of hemorrhagic cysts is difficult because cysts often appear hyperdense by computed tomography (CT) or have high density signal by magnetic resonance imaging (MRI) which is indicative of blood and/or high protein content within the cyst (7). Treatment is conservative with bed rest and pain management for 2-7 days (51). Occasionally, clot retention can lead to urinary tract obstruction which produces renal colic (51). In these cases patients are treated for longer periods of bed rest, intravenous hydration, and narcotics. Nonsteroidal anti-inflammatory drugs (nsaids) are efficacious for pain management; however, their longer term use can accelerate renal dysfunction and, thus, should generally be avoided (51). If symptoms, specifically pain, hematuria, and fever, last more than 7 days or if this is first episode for a patient over the age of 50 years old, renal carcinoma should be entertained in the differential diagnosis (52).

Cyst infection typically presents with unilateral or bilateral diffuse flank pain associated with fever. Urinalysis may be indicative of infection, but, as with cyst hemorrhage, a walled off infected cyst isolated from the urinary tract may produce a falsely normal urinalysis (51). Upper urinary tract infections are believed to be caused by lower urinary tract infections since (a) the former are commonly caused by enterobacteriaceae, the etiologic agent of lower urinary tract infections and (b) most occur in women, as do lower urinary tract infections (53,54).

However, hematogenous spread to cysts of ADPKD kidney has also been reported (53).

Identifying infected cysts pose a diagnostic challenge as CT and MRI are not able to consistently distinguish between infected and uninfected cysts (7,55,56). Nuclear imaging has been advocated (^{67}Ga or ^{111}In) to localize the source of infection, but false positive and negative results are common (54,57). A recent case series suggests utilizing 18-F-fluorodeoxyglucose as a marker for positron emission tomography (PET) scanning since inflammatory cells consume large quantities of glucose (58). Structural studies, like CT and MRI, in combination with functional studies, such as ^{67}Ga , ^{111}In , and 18-F-fluorodeoxyglucose, may more accurately identify infected cysts; however, no such study has been done to date.

Because cyst infections produce an abscess-like space in the kidney, antibiotic penetration into the cyst directed against the offending organism is necessary to resolve the infection. Schwab *et al* found that 15/26 (58%) of cyst infections persisted after five days of antibiotic therapy suggesting they are difficult infections to eradicate (54). Fluoroquinolones, trimethoprim-sulfamethoxazole, ampicillin or chloramphenicol are the currently recommended empiric antibiotics of choice because of their ability to achieve high intracystic concentrations, but the final antibiotic chosen should be based on results of blood, urine, and tissue culture (59-62). Finally, if antibiotic therapy does not resolve the infection, surgical or radiologically-guided drainage of the offending cyst is required.

Nephrolithiasis in ADPKD is comprised mostly of uric acid and calcium oxalate stones which affect 20-34% of patients (63,64). Development of stones is related to an acidic urinary pH, presumably due to a defect in urinary ammonia production, urinary citrate production, and urinary stasis secondary to anatomic damage (63). Grampsas *et al* demonstrated that cyst number and cyst volume were also associated with a greater risk of developing kidney stones (65). The diagnosis of nephrolithiasis is made by CT, and, if parenchymal calcification cannot be distinguished from urinary tract stone, then an excretory urogram can be utilized to delineate the location (66). Urologic management includes shock lithotripsy, or percutaneous nephrolithotomy which are similar therapeutic modalities utilized in patients with non-ADPKD related nephrolithiasis (66,67).

The risk of renal carcinoma in the ADPKD population is not different from that of the non-ADPKD population, and in ADPKD patients on dialysis, the risk is the same as patients with acquired cystic kidney disease (52). These patients commonly present with flank pain, hematuria and fever which can easily be confused with cyst infection or hemorrhage (52). The identification of carcinoma from among the many renal cysts is difficult. Contrast enhanced CT scan is the primary diagnostic modality, but cyst hemorrhage and infection can simulate carcinomas. Some investigators suggest that attenuation

coefficients of >30 HU in pre-enhanced images and attenuation coefficients of >95 HU in contrast enhanced images by CT to be highly suspicious of carcinoma (68). If CT is not diagnostic then MRI is recommended (69). While the incidence of renal carcinoma is not different from the general population, the biologic behavior appears altered with a higher incidence of bilateral, multicentric, and sarcomatoid types of renal carcinoma (52). These identified differences partly reflect the selection biases and limitations of the retrospective studies from which most of the carcinoma data is derived.

The initiation and progression of renal cyst growth not only results in complications like cyst hemorrhage, pain and infection, but is primarily responsible for the development of renal failure in ADPKD patients (17). In a seminal study to define the relationship between cyst development and renal failure, 232 non-azotemic ADPKD patients underwent annual MRI imaging to assess cyst and kidney volume, and renal function testing over a period of three years (17). Kidney and cyst volume increased exponentially during the three years of follow up; average initial kidney volumes of 1060 ml increased by 204 ml by the end of the study with an annual increase of 63 ml/year (or 5.3%) (17). Baseline kidney volume predicted the progression of kidney disease. Thus, individuals with the greatest initial kidney volumes (>1500 ml) lost renal function at the greatest rate (17). *PKD1* related ADPKD presented with greater kidney volumes, cyst volumes, and cyst number than patients with *PKD2* (70) and showed greater increases in total kidney volume (245 ml in *PKD1* vs 136 ml in *PKD2*) by the end of the observation period (17). *PKD1* mutants tended to lose renal function faster than *PKD2* mutants ($p=0.06$) (17). Men also developed greater increases in kidney volume and cyst volume than women (70). Other risk factors for progressive renal disease in ADPKD include black race, development of hypertension before the age 35, hyperlipidemia, sickle cell trait, and episodes of hematuria before the age of 30 (12,13,71).

3.2.3. Extra-renal Manifestations

3.2.3.1 Hepatic cysts

Hepatic cysts in ADPKD are derived from hyperplastic embryonic intrahepatic bile ducts that fail to normally involute. Biliary cystic epithelia separate from the bile ducts from which they were derived, but retain characteristics of the bile duct epithelia, such as responding to secretin (72).

Hepatic cysts are common in ADPKD. In a prospective cohort of young non-azotemic ADPKD patients, investigators found an overall prevalence of hepatic cysts of 83% (73). As with renal cysts, the prevalence of hepatic cysts increases with age from 58% in individuals of 15 to 24 years old to 94% in individuals of 35 to 46 years old (73). Kidney volume and renal cyst volume is also associated with the prevalence of liver cysts (73). The prevalence of hepatic cysts is similar between men and women (79% and 85%, respectively); however, cyst volume is greater in women than men (5.27 ml versus 1.94 ml; $p<0.05$), and 9.6% of women develop hepatic

cysts of greater than 1 L, but men do not (73). These prospective observational data confirmed what other investigators found in retrospective and cross-sectional studies that hepatic cystic disease is more severe in women than men. Hepatic cyst growth is believed to be estrogen responsive based on the larger cyst volumes seen in women, and pronounced cyst development in women with multiple pregnancies or those taking oral contraceptives (74,75).

Most often hepatic cysts are asymptomatic, but in cases of massive cyst growth, which occur commonly in women, they can cause chronic upper abdominal pain and early satiety and nausea by compressing the gastrointestinal tract (76). Cyst enlargement can compress the biliary tree producing obstructive jaundice, compress the portal veins producing portal hypertension and ascites, and compress the intrahepatic veins inducing ascites and lower extremity edema (76). Typically, these compression syndromes are treated with surgical cyst reduction and fenestration (76). Newer, less invasive radiologic measures include percutaneous transcatheter hepatic artery embolization which is able to reduce liver and cyst volume by approximately 2 L (77). Even with massive cyst enlargement, liver function usually remains normal (78). Thus, liver transplantation is limited to those with unrelenting life threatening complications of hepatic cysts.

As in the case of renal cysts, hepatic cysts can be complicated by hemorrhage and infection. Cyst infection is the most serious complication and so should be identified and treated aggressively. Patients typically present with right upper quadrant pain, fever, and leukocytosis. Blood cultures are positive in ~63% of cases (79), and with needle aspiration of the infected cyst, identification of the causative organism is found in approximately 86% of cases (76). Cyst infection is most often due to monomicrobial gram negative organisms (79). Identifying the infected cyst, as with renal cysts, is difficult. Investigators recommend utilizing CT looking for air-fluid levels, gas bubbles, cyst wall calcification, and heterogenous appearance of cystic fluid; although these signs are suggestive of infection, none are pathognomonic (80,81). ⁶⁷Ga, ¹¹¹In-labelled leukocyte scan, and ¹⁸F-fluorodeoxyglucose PET have also been used to localize infected hepatic cysts (58,82-84). Treatment includes appropriate antibiotics and percutaneous drainage. In cases where the offending organism is not yet identified ciprofloxacin is the treatment of choice because of its gram negative coverage and high intracystic concentration (79).

3.2.3.2. Vascular complications

Vascular complications are probably the most frightening to patients and the most concerning to physicians because, depending on their size and location, can cause unexpected death and disability. Classically, ADPKD is associated with intracerebral aneurysms (ICA), but it is also associated with other vascular abnormalities including intracranial arterial dolichoectasia (elongation and dilation of the artery), coronary aneurysms, abdominal aortic aneurysms and dissection of the thoracic aorta (85-91).

ICAs occur in 16% of ADPKD patients with a positive family history and in 6% of patients without a family history (92). Indications for ICA screening is controversial and is dependent on the assumptions that are made regarding the prevalence and natural history of ADPKD related ICAs (92). Either helical CT with contrast or MR angiography (MRA) are utilized to screen since both are able to identify aneurysms; however, sensitivity of either exam falls as the aneurysms decrease in size (93,94). MRA has become the screening exam of choice since it does not require iodinated contrast (92). Because surgical treatment, either coil embolization or clipping, places patients at high post-operative neurologic risk, the goal of screening is to identify patients at high short term neurologic risk, treat them, so as to improve the long term functional status (92,95). Some investigators suggest screening young individuals (between 18-35 years old) who have a family history of ICAs because it would identify (a) a high risk group and (b) a group where life can be significantly prolonged (96). If the screening CT or MRA is negative, a follow-up study should be performed every 5 years (96). A retrospective study found that only 2.6% of ADPKD patients with a negative initial screening test for ICAs were found to have an ICA after a mean of 9.8 years of follow up (97). This cohort was of only moderate risk because it included 43% with a family history of ICA or ruptured ICA and 57% without a family history of ruptured ICA (97).

If patients are found to have ICAs on screening exam, then an angiogram is recommended as the gold standard to determine size of the lesion (96). If the ICA is < 6 mm then follow up examination is suggested every two years (96). The screening and treatment recommendations are based on ICAs in non-ADPKD patients since the natural history of ADPKD related aneurysms is not known (96). That being said, a retrospective study illustrated that larger aneurysms are at greater risk for rupture, but that 52% of ruptured aneurysm occurred in patients with ICAs <10 mm (98). The ICAs greater than 6 mm are treated with surgical clipping or coil embolization (96). In sum, screening and treatment guidelines for ICAs in ADPKD are recommendations and, thus, remain a topic for debate since the natural history of these ADPKD related ICAs remain unknown (92). Until a randomized treatment trial of ICAs in ADPKD is completed, clinicians will likely need to follow recommendations developed from non-ADPKD ICA population.

3.2.3.3. Miscellaneous

Cysts have been found in pancreas, arachnoid membrane, and seminal vesicles at a prevalence of 5%, 8%, and 39%, respectively (99-103). Generally, these cysts are asymptomatic.

Mitral valve prolapse is a common cardiac complication occurring in ~25% of patients with ADPKD (104,105).

Histologic examination demonstrates myxomatous degeneration and disruption of collagen which suggests abnormalities of the extracellular matrix (106). Routine echocardiographic screening is not recommended unless a clinical sign such as a murmur develops.

Table 2. Blyth and Ockenden classification of ARPKD

Group	Clinical Presentation	Kidney histopathology
Perinatal	Bilateral large kidneys	>90% dilated tubules
Neonatal	Bilateral large kidneys	~60% dilated tubules
Infantile	Bilateral large kidneys with hepatosplenomegaly	~25% dilated tubules
Juvenile	Primarily Hepatosplenomegaly	<10% dilated tubules

From Ref 112

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPKD)

4.1. Genetics

ARPKD is caused by mutations of the *pkhd1* (polycystic kidney and hepatic disease 1) gene located on human chromosome 6p which encodes the protein fibrocystin/polyductin (107,108). The gene consists of 87 exons which form many alternatively spliced variants, but the longest transcript encodes the fibrocystin/polyductin protein which is generated from 67 exons and produces a 4074 amino acid protein (107,108). The physiologic role of fibrocystin is not known, however, experimental data suggest that it may act as transmembrane receptor or ligand, and functions to regulate collecting duct and biliary epithelial differentiation (109-111).

As the name implies the disease requires mutations in both *pkhd1* alleles in order to develop phenotypic disease. Intrafamilial variability is not as pronounced as in ADPKD. Utilizing a diagnostic classification system based on age at presentation (perinatal, neonatal, infantile, and juvenile), Deget et al compared 20 sibships and found concordant phenotypic expression in 17 (or 85%) of sibships (112,113). On the other hand, Bergmann et al studying 48 pedigrees with more than one affected child found that 28 families maintained concordant phenotypes amongst siblings (114). Together, these two studies included total of 68 ARPKD sibships in which intrafamilial phenotypic variability occurred in ~34% (23/68) of the pedigrees (113,114).

Three hundred and five unique mutations have been described in 700 mutant alleles; without a specific mutational "hot spot" identified within the gene (115,116). However, specific populations may have an increased frequency of particular mutations; for example, in individuals of Northern European origin, the T36M mutation is found in 17% of mutant alleles (116,117). This mutation may reflect an ancestral mutation (116,117) or may reflect a mutational "hot spot" since it has recently been found in unrelated ethnic groups (114,118). Most individuals with ARPKD are compound heterozygotes (different mutations at each allele) reflecting the heterogeneity of *pkhd1* mutations found within the population. Though no strict genotype-phenotype correlation exists, in general, homozygous truncating mutations are associated with early/perinatal renal manifestation of ARPKD while homozygous missense or a missense and truncating mutations present with a milder, delayed renal phenotype (115,116,118-120). Commonly, patients that survive the renal complications develop congenital hepatic fibrosis. In contradistinction to

mutations causing aggressive early renal disease, the mutations associated with liver disease tend to have either homozygous missense mutations or one missense and a truncation mutation, like the milder renal phenotype (115,118,121). In sum, truncating mutations induce a severe, perinatal renal phenotype and increase mortality, while missense mutations tend to generate a milder renal phenotype with more prominent hepatic phenotype.

4.2. Clinical Manifestations

4.2.1. Epidemiology

ARPKD is one of the most common hereditary renal diseases in the pediatric population with an incidence of 1:20,000 and a carrier rate of 1:70 (122).

4.2.2. Renal Manifestations

ARPKD classically presents in newborns with large palpable kidneys, oligohydramnios, and pulmonary hypoplasia. Neonatal pulmonary insufficiency is the primary cause of mortality in these patients, though many of these survivors will develop renal insufficiency. Blyth and Ockenden in 1971 developed a classification system which attempted to define the spectrum of ARPKD disease and focused primarily on the date of presentation of renal disease (Table 2) (112). The perinatal and neonatal presentations of ARPKD were associated with a 28 day mortality rate of ~80% (56/69), the majority of which was caused by respiratory insufficiency due to pulmonary hypoplasia (123). A small minority of these early deaths were attributed to chronic renal failure (123). Though this early study detected a high mortality rate with perinatal/neonatal presentations, patients were selected, partly, using death certificates which biased the study toward its high death rate (123). On the other hand, recent investigation shows that the five year survival rate is ~75% even in populations where the majority of cases studied were of the perinatal/neonatal renal phenotype (124). Nonetheless, significant mortality occurs during the first year of life (8-22%) (124). The risk of death is associated with a younger age at diagnosis and the development of chronic renal failure (124).

Chronic renal failure is a common complication affecting 33-72% of ARPKD patients with 8-29% developing ESRD (114,121,124,125). In a North American cross-sectional study of ARPKD patients, Guay-Woodford et al divided ARPKD patients into two cohorts: (a) an old cohort (born before January 1990) and (b) a young cohort (born after January 1990). Overall, the younger cohort was diagnosed much earlier (median 1 day) with ARPKD than the older cohort (median 72 days). Though most investigators find that patients with a perinatal/neonatal diagnosis of ARPKD are at the greatest risk of ESRD, these investigators reported that chronic renal failure to be equal between the old and young cohorts at ~40% in each group, but that the older group (diagnosed later) was at much greater risk for ESRD than the younger group (diagnosed earlier) (114,121,124,125). This increased ESRD risk is presumably related to lead time bias in older cohort who lived longer with chronic renal failure and, thus, had more time to develop ESRD than the younger cohort (124). In sum there is variability in the development of renal

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insufficiency and its progression to ESRD, but patients with a perinatal presentation, commonly with large cystic kidneys, are at greater risk of developing chronic renal failure, and, presumably, ESRD.

Hypertension is a prevalent manifestation occurring in 65-80% of patients and typically develops before renal impairment is apparent, but is commonly associated with progressive renal dysfunction (114,124-126). As in ADPKD, prospective trial-based evidence is lacking regarding the optimal BP goals and the role of RAS inhibition in reducing the risk of ESRD in ARPKD (127). However, laboratory-based evidence points to an activated intra-renal RAS, as well as enhanced Na absorption, that suggests that ACEi and/or ARBs may be efficacious (128-131).

Hyponatremia is observed variably (15-24%) and is seen from birth until ~4 months of age (124-126). Ninety six percent of those patients who reported a history of hyponatremia also reported a history of hypertension in a cross-sectional study of ARPKD patients (124). The relationship between hyponatremia and hypertension is interesting, especially, because genetic disorders of sodium balance can lead to hypertension (eg Liddle's syndrome) or hypotension (eg pseudohypoaldosteronism). However, the mechanism underlying hyponatremia and hypertension, and their relationship to each other, remains speculative.

As in the adult form of ADPKD, ARPKD has been associated with a urinary concentrating defect. Gagnadoux *et al* and Kaarinainen *et al* found that 96% (22/23) and 82% (9/11) of ARPKD patients developed significant impairment in urinary concentrating ability ($U_{max} < 550$ mosm), without progressing to massive polyuria (123,132). The concentrating defect is believed to be caused by diminished medullary interstitial tonicity, partly related to low aldose reductase expression (133).

ARPKD kidneys maintain their reniform shape, but lose their cortico-medullary differentiation. By ultrasonography patients have enlarged echogenic kidneys with or without small cortical cysts (124). Histopathologically, the kidneys are characterized by dilated ectatic collecting ducts which are radially arranged (134). As opposed to ADPKD where these cystic regions ultimately bud off and separate from the nephron, the cysts, or dilated tubules, remain contiguous with the filtering nephron in ARPKD (134,135).

4.2.3. Extra-renal Manifestations

The classic hepatic lesion found associated with ARPKD is the ductal plate malformation where dilated irregular bile ducts form a disrupted ring around the portal tract, usually without a centrally located bile duct. Collagenous proteins deposit along the portal tracts which eventually results in bridging fibrosis between portal tracts, but does not disrupt the acinar architecture of the liver. This pathologic entity is known as congenital hepatic fibrosis, and typically presents with portal hypertension, at times complicated by ascending cholangitis, but without hepatocellular dysfunction (136). Other patients develop

bile duct cysts, known as Caroli's disease, in association with congenital hepatic fibrosis which can lead to similar clinical syndromes of portal hypertension and cholangitis (136).

Hepatic disease is commonly found in association with ARPKD cystic renal disease, but tends to be less prominent clinically when the renal disease is more pronounced and more prominent clinically when the renal disease is less pronounced (115,125). Patients diagnosed with ARPKD later in life often present with hepatic symptomatology including portal hypertension and variceal bleeding (121,124). These patients may require liver transplantation classically for unremitting variceal bleeding, portal hypertension, and recurrent cholangitis, not for hepatic dysfunction (124). Overall, symptomatic liver disease is found in 15-46% patients of ARPKD patients; however, the prevalence of asymptomatic hepatic disease may be higher (124).

Liver function tests are normal in most patients as hepatocellular dysfunction is not a prominent complication of congenital hepatic fibrosis. A clue to the early development of portal hypertension is cytopenias on the complete blood count or hepatosplenomegaly on physical examination (136). Abdominal sonography is a reliable method to screen for portal hypertension and biliary abnormalities. If specific biliary abnormalities are seen, MR cholangiogram can be performed to delineate the biliary anatomy (eg biliary atresia). If portal hypertension develops and is complicated by varices, patients may require banding or sclerotherapy as treatment. However, other experts advocate for portosystemic shunting to decompress the portal system, especially since hepatocellular dysfunction is not common in ARPKD (136). Because controlled trials have not been performed in children, management of congenital hepatic fibrosis induced portal hypertension is dependent on the expertise of local medical center, surgeon, and gastroenterologist.

5. NEPHRONOPHTHISIS (NPHP)-MEDULLARY CYSTIC KIDNEY DISEASE (MCKD) COMPLEX

NPHP-MCKD complex is a spectrum of renal cystic disease characterized clinically by polyuria, polydipsia, chronic renal failure, and normal to small sized kidneys with corticomedullary cysts (137). Histopathologically, there is prominent tubulointerstitial fibrosis (137). However, critical differences between NPHP and MCKD include (a) early onset of renal failure in NPHP compared to MCKD, (b) autosomal recessive inheritance of NPHP versus autosomal dominant inheritance of MCKD, and (c) absence of extra-renal manifestations in MCKD other than hyperuricemia (138).

5.1. Nephronophthisis (NPHP)

5.1.1. Genetics

Positional cloning has identified seven genes (*NPHP1*, 2, 3, 4, 5, 6, and *AHII*) which are implicated in the phenotypic expression of NPHP (139-146). Mutations within a specific gene produce a classic presentation of NPHP, like mutations of *NPHP2* result in infantile NPHP

Table 3. Clinical manifestation of NPHP-MCKD complex

Group	Affected Gene	Median Age (years) at ESRD (ref)	Retinitis pigmentosa	Neurologic		Hepatic Fibrosis	Hyperuricemia
				JS ¹	CS ²		
Infantile	NPHP2	3 (141)	+	-	-	-	-
Juvenile	NPHP1	13 (150,221)	+	+	+-	-	-
	NPHP5	13 (150)	+	-	-	-	-
	NPHP6	11 (144)	+	+	-	-	-
Adolescent	NPHP3	19 (142)	+	-	-	+	-
	NPHP4	22 (143,222)	+	-	+	-	-
Adult	MCKD1	62 (137)	-	-	-	-	+
	MCKD2	32 (137)	-	-	-	-	+

Abbreviations: ¹Jouberts syndrome, ²Cogan syndrome

(see Table 3); however, at the level of each locus, significant variability exists in the progression to renal failure and in extra-renal manifestations. Further discussion of the clinical syndromes associated with particular loci will be discussed later.

5.1.2. Clinical Manifestations

5.1.2.1. Epidemiology

The incidence of NPHP is variable with 1:50,000 live births reported in Canada and 1 case per million reported in the US (147,148). Although a rare disease, it is the most common hereditary cause of ESRD in children in Europe with prevalence rates of 10-15%, while in North America it accounts of ~5% of children with ESRD (138).

5.1.2.2. Renal Manifestations

Classically, NPHP presents in three forms; (a) infantile, (b) juvenile, and (c) adolescent forms based on the age at which renal failure develops. Typical signs and symptoms include the inability to concentrate urine, polyuria, polydipsia, secondary enuresis, and anemia (149). An emblematic complaint is of waking at night due to thirst. Development of these signs portends the development of chronic renal failure and progressive renal disease. Renal sonography reveals kidneys that are of small to normal size with corticomedullary cysts. Of significance is that patients characteristically lack hypertension, lower extremity edema, and a history of urinary tract infections (149). The dearth of genitourinary symptomatology leads to a delay in diagnosis and often results in patients who present with advanced renal failure. Typical biopsy findings in early kidney disease include thickening and disruption of the tubular basement membrane, disproportionate tubulointerstitial fibrosis with little inflammatory infiltrate, cysts at the cortico-medullary junction, and tubular atrophy. There is invariable progression of kidney disease to ESRD, but the time course in which this occurs is variable. The affected loci, the type of mutation, and other environment and genetic factors contribute to the rate of progression of kidney disease (Table 3).

5.1.2.3. Extra-renal Manifestations

The association of retinitis pigmentosa with NPHP is defined as the Senior-Loken syndrome (SLS). It is observed sporadically (~10%) in patients with homozygous mutations of *NPHP1-4*, but without evidence for genotype-phenotype correlation (138). Retinal disease in association with *NPHP1-4* can present with early-onset or a late-onset SLS. The early-onset form of SLS is

characterized by coarse nystagmus and/or blindness at birth and up to the first two years of life (138). The late-onset form typically presents with night blindness and then overt blindness during school age. Fundoscopic abnormalities are detected by 10 years of age in all patients with SLS (138). While SLS occurs sporadically in association with certain NPHP loci, homozygous mutations of *NPHP5* and *6* exhibit early onset of retinitis pigmentosa in all cases (144,150) (Table 3).

Specific neurologic manifestations in the setting of NPHP comprise Jouberts syndrome. Patients with this syndrome exhibit coloboma (defect or gap) of the eye (with or without retinal degeneration), aplasia or hypoplasia of the cerebellar vermis leading to ataxia and mental retardation, polydactyly, cleft lip/palate, and episodic tachypnea and dyspnea. The “molar tooth sign” seen by MRI is the pathognomonic finding of Jouberts syndrome (138,151). Mutations of *NPHP1*, *AHII*, and *NPHP6* have been associated with Jouberts syndrome of nephronophthisis (144,145,151-153).

Related to disorders of the cerebellar vermis is the oculomotor apraxia of the Cogan syndrome which refers to the transient inability for horizontal eye movements during the first few years of life (138). The Cogan syndrome may or may not be found with Jouberts syndrome, and is found with mutations of *NPHP1* and *NPHP4* (154,155).

Hepatomegaly and portal fibrosis with mild bile duct proliferation is associated with NPHP, but differs from classic congenital hepatic fibrosis because of the less prominent bile duct proliferation (156,157). The relationship of hepatic abnormalities to NPHP is not as well established as with the neurologic syndromes, but recently, mutations of *NPHP3* have been associated with hepatic fibrosis and retinitis pigmentosa (Table 3) (142). Cone-shaped epiphyses of the phalanges are observed in NPHP in association with retinal degeneration and cerebellar ataxia, and are known as the Mainzer-Saldino syndrome (158).

Of interest, situs inversus was described in infantile NPHP (*NPHP2*) which suggested that the protein product of the gene, known as inversin, is important in left-right axis patterning (141). Utilizing a murine model of mutant *NPHP2*, these investigators recapitulated situs inversus suggesting that inversin is indeed involved in left-right axis specification (159).

There are many other syndromes described with NPHP which are beyond the scope of the review.

5.2. Medullary Cystic Kidney Disease (MCKD)

5.2.1. Genetics

MCKD is inherited in an autosomal dominant pattern with two identified genetic loci, *MCKD1* and *MCKD2*, localized to human chromosomes 1 and 16, respectively (137). Additionally, recent evidence suggests that mutations of uromodulin (*UMOD*) which encodes Tamm-Horsfall protein, can reproduce the MCKD phenotype as well as its autosomal dominant pattern of inheritance (160,161).

5.2.2. Clinical Manifestations

5.2.2.1. Epidemiology

MCKD is a rare disease with more than 50 cases reported by 2001 (149). It has been described in many kindreds around the world, but mainly in Europe and North America (149).

5.2.2.2. Renal Manifestations

As with NPHP, these patients present with isosthenuric urine, polyuria, polydipsia and anemia which reflects the prominent tubulointerstitial fibrosis seen with this disorder. Proteinuria and hematuria are uncommon. Macroscopically, the kidneys are normal to small in size with a loss of the normal cortico-medullary boundary. Late in disease medullary cysts develop. The kidneys display prominent interstitial fibrosis, tubular atrophy, and thickening of the tubular basement membrane, features that are consistent with NPHP. MCKD differs from NPHP in three distinct ways; (a) MCKD is inherited in an autosomal dominant fashion, (b) MCKD typically results in ESRD after the third decade of life, and (c) MCKD has no other extra-renal manifestation other than hyperuricemia with or without gout (see Table 3) (138).

5.2.2.3. Hyperuricemia

As with MCKD, familial juvenile hyperuricemic nephropathy (FJHN), due to mutations of *UMOD*, is inherited in an autosomal dominant pattern, is associated with hyperuricemia, and is associated with the development of renal failure (149). In general MCKD patients develop ESRD after 30 years of age while many FJHN patients develop renal failure between the second and fourth decades of life (162). Pathologically, the diseases are similar except that FJHN patients develop renal cysts less frequently than do those with MCKD (163). The hyperuricemia of FJHN is associated with a low fractional excretion of uric acid ($FE_{ur} < 5.1\%$), a biochemical abnormality not seen in MCKD (160,162,164). Clinically, FJHN do not develop impaired urinary concentrating ability until late in disease, while impaired urinary concentrating ability is an early sign and symptom of MCKD (162).

6. BARDET-BIEDL SYNDROME (BBS)

6.1. Genetics

BBS is an autosomal recessive disease with up to twelve genes (see Table 1) implicated in its pathogenesis (165). Though recessively transmitted, evidence suggests that at least some phenotypes of BBS are caused by triallelic inheritance (166-168). Triallelic inheritance

requires three mutant alleles to be present in order to express the phenotype. Two mutant alleles are found at one locus (homozygote or compound heterozygote at one locus) and the third mutant allele is expressed at a second locus (heterozygote) (169). This type of inheritance has led investigators to propose that the disease is passed in a recessive manner, and the third allele acts as a modifier of phenotypic penetrance. On the other hand, Smaoui *et al* studied *BBS2*, *BBS4*, and *BBS6* genes in patients with known biallelic mutations at *BBS1*, but found no mutations at the other loci. They concluded that homozygous and/or compound heterozygous mutations at a single locus were sufficient to induce the BBS phenotype (170). In sum, the BBS phenotype is inherited in a classic autosomal recessive manner, but also may be transmitted through a more complex triallelic pattern.

6.2. Clinical Manifestations

6.2.1. Epidemiology

The prevalence of BBS varies amongst different populations throughout the world, relying on high rates of consanguinity for phenotypic expression. For example in Newfoundland and the Bedouin of Kuwait the prevalence of BBS is 1:17,500 and 1:13,500 live births, respectively, while in the United Kingdom and Switzerland it is much lower at 1:125,000 and 1:160,000 live births, respectively (171-174).

6.2.2. Renal Manifestations

Structural and functional abnormalities of the kidney are common findings seen in 46-100% of BBS patients (172,175,176). Fetal lobulation, calyceal cysts and diverticula, microcysts, diffuse cortical loss, and focal scarring are all structural features associated with BBS, and are found more commonly than impairment of glomerular filtration rate (172,175,177). Chronic renal failure, with progression to ESRD, is present in anywhere from 5 to 30% of patients (172,175,176,178). As in other cystic renal diseases, 70% of patients are unable concentrate their urine to greater than 750 mosm/Kg (179,180). In addition a defect in the ability to maximally acidify the urine was observed in 35% of patients (179).

First degree relatives of BBS patients have a higher incidence of renal cell carcinoma (181). Genetic analysis of renal carcinoma tissue isolated from first degree relatives demonstrated a loss of heterozygosity at several BBS loci implicating BBS in the pathogenesis of renal cancer (181). The risk of cancer in BBS patients is not well defined, but a high index of suspicion is warranted based upon the risk seen in their obligate carriers.

6.2.3. Extra-renal Manifestations

The classic manifestations include retinal dystrophy leading to significant blindness by 15 years of age, polydactyly, central obesity believed to be related to hyperphagia, mental retardation, hypogonadism in males, and structural/functional renal abnormalities (Table 1) (176). Criteria have been developed to diagnose BBS (Table 1) as many patients are diagnosed late in life because of the delayed appearance of signs and symptoms. Beales *et al* suggested that identification of retinal dystrophy is the most successful

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marker for early identification of BBS because of its high frequency and early presentation (before 10 years of age) (176). Identification of strabismus and myopia, as they usually precede retinal changes, can alert the physician to investigate this diagnosis. As of 1999, the average age of BBS diagnosis was 9 years old; the fact that parents first noted abnormalities in their children by 3 years of age suggests a six year delay in diagnosis from initial presentation (176). Thus, vigilance regarding early symptoms, in addition to clear diagnostic criteria and education about this rare disease, will hopefully provide a greater opportunity for earlier identification.

In a study of the natural history of BBS, 38 affected and 58 unaffected siblings were studied over a period of 6 years (175). 86% of the affected were legally blind, 88% were obese, 66% were hypertensive, and 32% developed diabetes while the unaffected siblings did not develop any of the above complications (175). 25% died by the age of 44 years old while 98% of the unaffected siblings survived (175). In sum, a high index of suspicion in individuals that develop diabetes, hypertension, obesity and blindness early in life may help to identify BBS patients, but also suggests that these patients should be treated aggressively (for diabetes, hypertension etc) as they have a high mortality rate.

7. ORAL-FACIAL-DIGITAL SYNDROME 1 (OFD1)

7.1. Genetics

OFD1, the gene implicated in oral-facial-digital syndrome type 1 (also known as Papillon-Geage-Psaume syndrome), is an X (Xp22.2-22.3)-linked dominant syndrome that causes intrauterine death in males (182-184). A single male *OFD1* patient survived to the perinatal period; this infant expressed an XXY karyotype which was "protective" because of heterozygosity at the *OFD1* locus (185). Females present with significant intrafamilial phenotypic variability based partly on skewed X-inactivation in tissues (186). In analyzing genotype-phenotype correlations, splice mutations are associated with cystic kidneys, mutations of exons 3, 8, 9, 13, and 16 are linked to mental retardation, and mutations in the coiled-coiled domains of *OFD1* are associated with tooth abnormalities (186). Sporadic OFD cases appear to be more common than familial cases (186).

7.2. Clinical Manifestations

7.2.1. Epidemiology

OFD type 1 is estimated to occur in 1:250,000 live births and in a variety of racial backgrounds (182,187). Racial background can influence the phenotypic expression of OFD. In the general population blacks have a lower incidence of cleft lip and cleft palate than Caucasians (187). Similarly, cleft lip and cleft palate is less frequently observed in black (25%) than in Caucasian (80%) OFD patients (187) suggesting the black OFD patients are resistant to abnormalities of the lip and palate even with a genetic disorder that predisposes them.

7.2.2. Renal Manifestations

PKD is a characteristic feature of this hereditary disorder and accounts for a significant portion of morbidity and mortality associated with the disease. PKD occurs in approximately 50% of OFD type 1 patients (186) and is often

asymptomatic so that it presents late in life. As an example of intrafamilial renal phenotypic variability, Scolari *et al* reported an OFD proband (perinatal diagnosis) who developed ESRD by 16 years of age due to OFD related PKD. The mother with mild extra-renal manifestations of OFD (cleft palate, clinodactyly (finger or toes permanently bent) of hands and feet, and patchy alopecia) was diagnosed with PKD at 45 years of age by renal sonogram. By 55 years of age, the mother had chronic renal failure with a serum creatinine 3.5 mg/dL (188). Because PKD may be absent at birth but is a common clinical manifestation, routine monitoring for the development of PKD is suggested.

PKD in OFD patients leads to ESRD after the second decade of life, but is variable (189). Renal sonography reveals kidneys of normal size and contour but with multiple small (<1 cm) cysts throughout the parenchyma (190). Histopathology of the cystic kidneys demonstrate distal tubular cysts, but also, distinctively, glomerular cysts (189,190).

7.2.3. Extrarenal Manifestations

The non-renal phenotypic manifestations of this disease are the clues leading to the clinical diagnosis of OFD type 1. As the name implies, oral, facial, and digital abnormalities are common. Oral features include cleft palate (80%), bifid or lobulated tongue (30-45%), small median cleft or pseudocleft of the upper lip (45%), hyperplastic buccal frenulae, lingual hamartomas (70%), hypodontia (fewer number of teeth than normal) and low lateral incisors (186). Facial features include hypertelorism (wide spaced eyes), broad nasal bridge, hypoplasia of the nasal alae, facial asymmetry and alopecia (186). Anomalies of the fingers (45%) and toes (25%) include brachydactyly, syndactyly, clinodactyly, and, less commonly, polydactyly (186).

Neurologic complications vary from normal intelligence to mental retardation (40%) (186). Neuro-anatomic (40%) abnormalities include agenesis of the corpus collosum, arachnoid cysts, cerebellar anomalies, porencephaly (lateral ventricle extends to cerebral hemisphere), and hydrocephaly (186,191). The disordered bone mineralization characteristic of OFD type 1 is evident from radiographs of the proximal and middle phalanges which show areas of reticulated radiolucencies interspersed with regions of spicule-like formations (192). This difference has been used to distinguish OFD type 1 from other OFD like syndromes (192).

The severity of the signs and symptoms are variable from person to person and from generation to generation. This makes identification difficult; however, a thorough family history and a careful physical exam should improve early identification of OFD, as genetic counseling will be needed for the affected individual.

8. MISCELLANEOUS HEREDITARY PKD SYNDROMES

8.1. ADPKD associated with Tuberous Sclerosis (TSC)

TSC is an autosomal dominant disease caused by mutations of either the *TSC1* (human chromosome 9) or

TSC2 (human chromosome 16) tumor suppressor genes (193,194). A second somatic mutation, as in ADPKD, leads to a loss of heterozygosity and induces tumor formation in brain, skin, retina, heart and kidney (195,196). Patients with mutations of *TSC1* tend to have milder disease than age-matched patients with *TSC2* mutations (197). TSC has a prevalence of 8 to 9 per 100,000 individuals with a high degree of penetrance (198). The variable location and tissue distribution of tumors primarily dictates the symptoms and manifestations of TSC. Thus, for example, central nervous tumors, like subependymal nodules, cortical hamartomas, are able to produce hydrocephalous, seizures, and mental retardation. Retinal hamartomas are found in eyes, rhabdomyosarcomas in the heart, and hypomelanotic macules, facial angiofibromas, ungula fibromas in the skin (199). The kidney is principally affected by angiomyolipomas, cysts, and renal carcinoma (197,200). Cysts affecting the kidney are a common complication occurring in 25% of TSC patients (197), but individuals with enlarged cystic kidneys presenting during infancy and resembling ADPKD are much less common (201). *TSC2* resides adjacent to *pkd1* on chromosome 16 so that large genomic deletions that cross both genes produce this aggressive infantile form of ADPKD in TSC patients (201). Although most patients with ADPKD associated with TSC present early in life, slowly progressive cystic renal disease may lead to renal failure in early adulthood (202).

8.2. ADPKD associated with von Hippel-Lindau

Von Hippel-Lindau is a rare autosomal dominant disorder which is found in 1:39,000 to 1:53,000 individuals (203). This syndrome is linked to mutations in the *VHL* tumor suppressor gene found on human chromosome 3 (204). As in ADPKD where secondary somatic mutations produce a loss of heterozygosity and subsequent cellular proliferation, somatic mutations of the normal *VHL* allele induce a growth advantage, but, unlike ADPKD, patients present with tumors (203,205,206). Central nervous system (cerebellar, brainstem, and spinal cord) hemangioblastomas are the classic findings of von Hippel-Lindau, but also observed are retinal angiomas, renal carcinomas (clear cell type), pheochromocytomas, pancreatic islet cell tumors, epididymal cystadenomas, renal cysts, pancreatic cysts and rarely hepatic cysts (203,207).

Renal cysts and renal cancers are present in 60% and 26%, respectively, of patients (203). Renal carcinomas are always of the clear cell subtype and are found bilaterally in greater than 50% of cases (205). Renal cysts are usually few and bilateral. They are present in most patients by the third decade of life. Generally, the cysts do not distort the normal architecture of the kidney and do not induce renal failure. However, cases have been reported where patients present with renal cystic disease, indistinguishable from ADPKD; but, upon further examination of the first degree relatives and/or radiologic exam of the proband, central nervous system hemangiomas were found which led to the diagnosis of von Hippel-Lindau (203,206). It is rare that cystic kidney disease associated with von Hippel-Lindau results in chronic renal failure, but renal insufficiency caused by nephrectomy for

treatment of renal carcinoma is common (205). In sum, polycystic kidney disease indistinguishable from ADPKD can present in patients with von Hippel-Lindau, but is an uncommon occurrence.

9. THERAPEUTICS IN PKD

To date, specific treatments for polycystic kidney disease, of any type, are lacking. Treatment is supportive and based on treatment guidelines for chronic kidney disease (208). However, new classes of therapeutics which include vasopressin type 2 receptor (V2) antagonists and older classes of medication, like somatostatin and sirolimus, are being studied as possible therapeutic agents for PKD, especially, ADPKD.

The use of V2 receptor antagonists for PKD is based on evidence that PKD renal epithelial cells (a) accumulate high concentrations of cAMP which stimulates proliferation and secretion, (b) express greater abundance of V2 receptor than normal cells and that (c) inhibition of V2 receptor reduces cellular cAMP concentrations (49,209). Utilizing rodent models of nephronophthisis (*PCY*), ARPKD (*PCK*), and ADPKD (*PKD^{tm1som}*, orthologous to human *pkd2*) V2 receptor antagonists have been shown to reduce cyst volume, kidney weight, renal fibrosis, and tissue cAMP abundance while improving renal function (49,210). As a proof of principle, simply boosting water intake in the *PCK* rodent model of ARPKD to suppress vasopressin levels diminished renal tubular proliferation and improved renal function compared to control *PCK* rats (211). An oral human V2 antagonist has been developed (Tolvaptan) that has completed phase II human clinical trials and will begin phase III clinical trials late in 2007 (7).

Octreotide, a synthetic isoform of somatostatin, also reduces cellular cAMP concentrations, a finding which has prompted interest in it as a treatment for PKD and cystic liver disease. Octreotide treatment of *PCK* rats inhibited hepatic and renal cyst growth suggesting a role for its use in the treatment of PKD (212). A small pilot human study in ADPKD patients showed that a long-acting somatostatin analogue was safe and that it tended to reduce the rate of renal cyst growth compared to placebo controls (213). Further clinical trials are ongoing to evaluate the effect of long acting somatostatin on hepatic cysts in ADPKD.

The kinase activity of mTOR is an important regulator of cell proliferation, growth, and metabolism, and is inappropriately activated in rodent and human models of PKD (214,215). Because PC-1 is believed to regulate mTOR activity, it is hypothesized that absent or mutant PC-1 leads to dysregulation of mTOR activity which induces proliferation and cyst formation (215). Treatment of *orpk* and *bpk* mice, murine models of ARPKD, with sirolimus, a specific mTOR inhibitor, diminished renal tubular proliferation, decreased kidney weight, and improved renal function compared to vehicle treated controls (215). A retrospective review of ADPKD renal transplant recipients treated with sirolimus revealed that native ADPKD kidney

volume decreased by approximately 25% while patients treated with alternate immunosuppressive medications showed no change in kidney volume (215). Similar studies in rodent models of ADPKD showed reductions in kidney weight and improvement in renal function when treated with sirolimus (216,217). As with the other new therapeutics for ADPKD, a phase III trial is underway to determine the therapeutic potential of sirolimus in ADPKD.

10. CONCLUSIONS

Hereditary PKD can present in many ways; (a) in isolation with primarily renal manifestations and complications or (b) in combination with extra-renal phenotypic features. Because cystic renal diseases are uncommon, early recognition is often difficult; however, a high index of suspicion can lead to important diagnostic, preventive and therapeutic measures which will ultimately improve morbidity and mortality. If cystic renal disease is recognized, vigilance in history taking and physical examination can improve the odds of making an accurate diagnosis as it not only impacts on the patient, but also first degree relatives of the index case. Molecular diagnostics remains mostly research tool at this time which emphasizes the importance of an accurate clinical diagnosis. Finally, these diagnostic considerations will become more important as new therapeutics designed for cystic kidney disease come to clinical practice.

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Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; ARPKD: autosomal recessive polycystic kidney disease; NPHP: nephronophthisis; MCKD: medullary cystic kidney disease; BBS: Bardel-Biedel syndrome; OFD: oral-facial-digital syndrome; TSC: tuberous sclerosis; ESRD: end stage renal disease; PC-1: polycystin-1; PC-2: polycystin-2; MDRD: Modification of Diet in Renal Disease; BP: blood pressure; GFR: glomerular filtration rate; MAP: mean arterial pressure; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; RAS: renin-angiotensin system; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin

receptor blocker; CT: computed tomography; MRI: magnetic resonance imaging; NSAIDs: nonsteroidal anti-inflammatory drugs; PET: positron emission tomography; ICA: intracerebral aneurysms; MRA: magnetic resonance angiogram; US: United States; SLS: Senior-Loken syndrome; JS: Jouberts syndrome; CS: Cogans syndrome; UMDO: uromodulin; FJHN: familial juvenile hyperuricemic nephropathy; V2: vasopressin type 2 receptor

Key Words: polycystic kidney disease, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, nephronophthisis, medullary cystic kidney disease, Bardel-Biedl syndrome, oral-facial-digital syndrome, tuberous sclerosis, von Hippel-Lindau, review

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