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Autosomal Dominant Polycystic Kidney Disease: A Comprehensive Review

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Abstract

Background and Aims: Autosomal dominant polycystic kidney disease (ADPKD) is a common cause of end stage renal disease and accounts for a substantial number of dialysis and transplant patients worldwide. Studies over the years have revealed precious information about the disorder's genetic profile, pathogenesis, systemic manifestations and its progression. An increased understanding of these aspects has enabled the development of clinical trials and potentially effective treatments.

Relevant data on this topic was procured and synthesized with the aid of a comprehensive Medline search in addition to nephrologic and urologic literature review on ADPKD. The article provides an in-depth review into the natural history and pathogenesis of ADPKD; various clinical manifestations; progression of the disease; accuracy, reliability and need of screening and diagnostic procedures in different age groups; and novel therapeutic approaches that are being evaluated in ADPKD.

Keywords: Polycystic Kidney, Autosomal Dominant

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic, multi-systemic disorder characterized by the development of renal cysts and various extra-renal manifestations. Although the disease begins in-utero, it may take several decades for the signs to surface and is a leading cause for end stage renal failure. It affects all ethnic groups worldwide with an estimated prevalence of approximately 1 in 800 live births (1). Being an autosomal dominant disorder, the offspring runs a 50% risk of inheriting the mutated gene. However, only about one half of these cases are diagnosed during their lifetime, as the disease usually runs an asymptomatic course (2).

Genetics

At least two distinct gene defects (possibly 3) have been identified in the pathogenesis of ADPKD – PKD 1 and PKD 2 (3).

Type 1 ADPKD caused by mutation in the PKD 1 gene accounts for nearly 85% of the cases with its causative gene localized to the short arm of chromosome 16 in the PKD1 locus (4). The PKD1 gene codes for polycystin-1 (PC1), which plays a vital role in cell-cell and cell-matrix interactions (5). Thus a defect in polycystin-1 leads to an alteration in the differentiation of epithelial cells and abnormal phenotypic expressions of ADPKD (6).

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Type 2 ADPKD caused by a mutation in the PKD 2 gene accounts for about 10-15% of the cases, with the defective gene located on chromosome 4 (7). The rest (around 5%) have a defect unrelated to either locations and may be accounted by spontaneous mutations. The PKD2 gene codes for polycystin-2 (PC2), which is involved in cell calcium signaling (8, 9). The occurrence of cysts and end-stage renal disease are delayed in PKD2 disease (mean age 74.0 as against 54.3 years in PKD1) (10).

The disease is characterized by a variable renal disease progression and manifestation. The variable phenotypic expression of the disease within families (intra-familial variability) is often linked to the occurrence of a somatic mutation in the intact allele within epithelial tubular cells (2nd hit hypothesis) (8, 11, 12). However the inter-familial variability can be accounted by genetic heterogeneity (PKD1 vs. PKD2). Genetic modifiers (any gene unlinked to the PKD1 or PKD2 loci whose genotype correlates with the ADPKD phenotype) also play a role as far as clinical manifestation and disease progression in PKD1 is considered (13).

Pathogenesis

The ability of human PKD cells but not normal renal epithelial cells to form cysts in culture points towards a genetic etiology that directly induces cyst genesis (14). A gene expression study using DNA micro arrays on disease modeled Pkd1L3/L3 mice identified differentially expressed genes that could account for both the generation of cysts and progression of disease (15).

The polycystin complex (PKD1 and PKD2 encoding polycystin-1 and polycystin-2 respectively) is implicated in the regulation of the cell cycle and hence holds the key in the pathogenesis of ADPKD (16). Studies suggest polycystin-1 (PC1) to be localized in primary cilium, tight junctions, adherens junctions, desmosomes and focal adhesions which stresses its role in maintaining cell-cell and cell-matrix interactions (5, 17). Thus a defective polycystin-1 would lead to abnormal epithelial cell differentiation and the various phenotypic expressions of ADPKD. Polycystin-2 (PC2) is a non-selective cation channel involved in cell calcium signaling and is localized to primary cilium, centrosome and endoplasmic reticulum (18).

A study using a lentiviral mediated-siRNA expression model of Pkd1 hypomorphism showed that loss of PC1 function is sufficient enough to produce centrosome amplification, multi-polar spindle formation and hence genomic instability (19). The centrosome, in turn, may have significant role in the regulation of cell-cycle progression and control.

Abnormal cellular differentiation, maturation and apoptosis have been held responsible for the formation of cysts via biochemical mechanisms that include:

1. Abnormal cilia function: As PC1 and PC2 localize to renal epithelial cilia, defects in renal cilia caused by mutations to either gene can contribute to renal cyst genesis (8, 11, 20, 21). Alterations in cilia function in polycystic kidneys may directly interfere with their mechano-sensory properties (16). Inability of renal epithelium to correctly sense luminal flow rates lead to deregulated tissue growth and renal cysts as a result of the polycystic kidney's attempt to compensate for a perceived lack of fluid flow (22). The connection between abnormal cell growth and defective cilia function can be further stressed based on the observation that cilia are connected to centrosomal structures (21). The centrosome, in turn has a significant role to play in the regulation of cell-cycle progression and control.

2. cAMP activation: Vasopressin V2 receptor antagonists were found to inhibit or arrest the progression of renal cystic disease in rodent models of human type 2 ADPKD suggesting a possible role of cAMP in cyst development (23). Recent studies have demonstrated cAMP to potentiate cyst genesis via stimulating the Ras/mitogen-activated protein

kinase (MAPK) pathway and by activating the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel (24). cAMP has also been implicated in increasing the B-Raf kinase activity and ERK phosphorylation in polycystic kidney cells (25).

3. Defective cell protein targeting: It has been noted that, some human PKD cysts have Na-K-ATPase pumps translocated to the luminal membrane, rather than limited to the basolateral membrane whereby promoting sodium and water secretion into the cyst and resulting in cyst growth (26).

4. Abnormal epithelial cell growth: Activation of proto-oncogenes and/or transcription factors, and subsequent tubular hyperplasia may play an important role in epithelial cell growth (27, 28). Over expression of oncoprotein prothymosin alpha was found to induce polycystic kidney disease in mice (28).

5. Angiogenesis: The role of angiogenesis in cyst growth and progression is supported by the observation that renal and hepatic cysts have elevated levels of vascular endothelial growth factor (VEGF) and other cytokines (29). The success of renal transcatheter arterial embolization (TAE) in renal contraction therapy in ADPKD patients also lends support to the pathogenetic theory of angiogenesis (30).

Cyst Development and Growth

De-differentiation of tubular epithelial cells resulting in their proliferation is the major element in the pathogenesis of ADPKD (31). Cysts start off as dilatations in intact tubules that are in contact with the nephron and fill by glomerular filtration (32, 33). The cysts have a predilection to arise from the distal nephrons and collecting ducts (34). As cysts grow, the cystic fluid is contributed more by transepithelial fluid secretion. This is also accompanied by interstitial inflammation, degradation of matrix components and hyperplasia of the cystic epithelium (35).

In a study to estimate the significance of gene type to disease progression, it was seen that the growth of cysts occurred at a consistent rate per individual, and that larger kidneys were associated with more rapid disease progression. Thus the genetic mutation in autosomal dominant polycystic kidney disease can be linked to the number of cysts (cyst initiation) and not to the rate of cystic growth (36). In another prospective study of 241 non-azotemic patients to assess the progression of the disease, it was found that though the PKD1 kidneys were larger and had more cysts than PKD2 kidneys in the baseline study, the rate of cyst growth in the two groups did not show any significant change (37, 38).

Renal Manifestations

Renal manifestations that can occur include:

Hypertension: This is a relatively early finding in ADPKD with an average onset at 30 years of age (39, 40). However, ambulatory blood pressure and left ventricular mass index in affected young adults seem to be more than their age-matched controls (41). Increased activity of the local intra renal renin-angiotensin system secondary to renal ischemia as a result of expanding cysts has been held responsible for rise in blood pressure (39, 40, 42). Defective polycystin function in the vasculature could also trigger the early development of hypertension as is evidenced by the expression of polycystins in the vascular smooth muscles and endothelium (43). Adequate control of hypertension can hinder disease progression with regard to renal volume, proteinuria, cardiovascular complications, and progression to end-stage renal disease. Hypertension can be effectively controlled by the use of ACE inhibitors or angiotensin II receptor blockers (44). Renal denervation has been found effective in reducing hypertension in murine models of the disease (45).

Urinary tract infections: Urinary tract infection is a common presenting symptom in ADPKD patients, with some having recurrent episodes and have been found to increase the rate of deterioration of renal function (46). Most may be accounted by the urinary

stasis caused as a result of the distorted renal anatomy (47). Urinary tract instrumentation often induces infection and needs to be avoided (48). Studies have also found the frequency of vesico-ureteral reflux to be higher in ADPKD children who report with urinary tract infections (49).

Hematuria: Gross hematuria is usually seen when enlarged cysts rupture into the collecting system and is usually preceded by a precipitating event such as a urinary tract infection, strenuous exercise or a flank injury (50). Hence participation in activities and sports in which abdominal trauma may occur should be strongly discouraged in them. Hematuria usually resolves in a weeks time with proper hydration and bed rest. Persistent bleeding may need percutaneous arterial embolization or even nephrectomy (51). Gross hematuria is more likely among individuals with larger kidneys, hypertension and higher plasma creatinine concentrations (50) and may reflect accelerated cyst expansion and rapid progression of kidney disease in ADPKD.

Hemorrhage into a cyst is more likely to present with pain than hematuria as many cysts do not communicate with the collecting system (52). Hematuria may also be caused by nephrolithiasis which usually resolves with the passage or removal of the stone. Prolonged or recurrent hematuria in the elderly is an indication to screen them for renal cell carcinoma, bladder carcinoma and IgA nephropathy (52, 53).

Concentrating defect: Most ADPKD patients have a mild sub clinical concentration defect which appear to worsen with age and may be associated with the disturbed tubular architecture or early tubulointerstitial disease (54, 55). However some clinically manifest with symptoms of polydypsia and polyuria (56).

Proteinuria: Proteinuria is usually minimal in ADPKD patients and is associated in patients with more advanced renal dysfunction (57). Proteinuria is not considered a major feature of ADPKD as secondary focal glomerulosclerosis plays a relatively minor role in most patients in the progression of this disorder to renal failure (58).

Nephrolithiasis: The prevalence of renal stones in ADPKD patients exceed that in the general population (59). One in every five ADPKD patient seems to be a stone former (60, 61). Urinary stasis associated with distorted renal anatomy tends to delay washout of crystals and increase the risk of urinary infections (47). This along with decreased urine volume, low urinary citrate and magnesium levels and less often, hyperuricosuria and hypercalciuria contribute to nephrolithiasis in ADPKD patients (59). Nephrolithiasis may be associated with acute flank pain with or without hematuria. Ultrasonography or intravenous pyelography may be used to detect stones. However, CT scan appears a superior diagnostic tool for small or radiolucent stones (61).

The distorted renal anatomy and infected cysts can complicate cystoscopy, percutaneous nephrostomy or extracorporeal shock-wave lithotripsy (ESWL) (60, 61). However, the size and location of the upper tract stones rather than the associated presence of polycystic kidneys may dictate the intervention modality adopted.

Pain: Persistent flank or abdominal pain is usually associated with enlarging kidneys and is thought to reflect either stretching of the capsule or traction on the renal pedicle (52). Patients may also complain of pain unrelated to the kidneys such as headache, chest pain or leg pain (62). Acute onset pain may however be suggestive of a superimposed complication, such as hemorrhage into a cyst, torsion or infection of a cyst, or an obstructing stone (63).

Non opioid analgesics [including non steroidal anti inflammatory drugs] used for short durations have been effective in reducing pain. However invasive management or the use of opioid analgesics may be considered in case of persistent pain that is severe enough to diminish the quality of life (64, 65).

Renal cancer: Renal tumors associated with ADPKD do not have an increased prevalence when

compared to the general population but are often bilateral at presentation, multi centric and sarcomatoid in type (52, 66). Rapid growth of a complex cyst or systemic signs and symptoms (fever, anorexia, fatigue, weight loss) that are out of proportion to the severity of the renal disease in the absence of renal infection should raise suspicions of renal malignancy (66). Percutaneous aspiration and cytological analysis, CT scan or MRI may be considered for an accurate diagnosis (67).

Extra Renal Manifestations

1)Cerebral Aneurysms: Altered expression and/or function of the PKD gene in arterial smooth muscle cells and myofibroblasts play an important role in the genesis of cerebral aneurysms (68). A ruptured cerebral aneurysm, resulting in a sub arachnoid or intra cerebral hemorrhage, is the most serious complication of polycystic kidney disease (69). The risks for an aneurysmal rupture include a family history of intracranial aneurysm or sub arachnoid hemorrhage, increasing size of the aneurysm, increasing age, and poorly controlled hypertension (70).

The efficacy of screening asymptomatic patients is unsettled. Routine screening is recommended only for high-risk patients, such as those with a previous rupture, a positive family history of an intra cerebral bleed or intracranial aneurysm, warning symptoms, a high-risk occupation in which loss of consciousness would place the patient or others at extreme risk, prior to anticoagulant therapy and prior to surgery that is likely to be associated with hemodynamic instability with hypertension (69, 71).

Screening utilizes high-resolution CT angiography (CTA) or magnetic resonance angiography (MRA) as the procedures of choice (72, 73). Cerebral angiography is invasive and is associated with an increased risk of intra cerebral bleed or cerebro vascular accident (72). The use of gadolinium during MR imaging has been strongly linked to nephrogenic systemic fibrosis and is hence not advisable in patients with an estimated glomerular filtration rate less than 30 ml/min.

Among patients who have aneurysms less than 7 to 10 mm in size, a follow-up monitoring is advisable for the next two to three years, and every two to five years thereafter if the aneurysm is clinically and radio graphically stable (74). However, newly detected small aneurysms may be reimaged at six months, and reverted back to longer imaging intervals if the 6 month study shows no significant change (75).

Among patients with initially negative radiographic studies, rescreening every five years among those with a family history of intra cerebral bleed or cerebro vascular accident (CVA) is advisable (76). In those with initially negative studies and no family history of CVA or bleed, the role of additional screening is unclear.

Indications for intervention: About 17% of sub arachnoid hemorrhages are preceded days or weeks before by severe headache (sentinel headache), caused by a small bleed or an unruptured aneurysm with wall changes (77). In view of the poor prognosis associated with a major sub arachnoid hemorrhage, an earlier diagnosis of a sentinel headache (also called a warning leak) appears very handy. CT scan is a safe and effective option in diagnosing a sub arachnoid hemorrhage or an intra cerebral bleed. However a negative CT scan should be followed in 6 to 12 hours by a lumbar puncture looking for xanthochromia and red cells. Arteriography should be performed if these findings are present. Aneurysms of any size associated with symptoms or those $\geq$7 to 10 mm in diameter or smaller cysts in patients with previous bleed may be corrected surgically or by endovascular repair, since these lesions have a high risk of rupture (75, 78). However they run the risk of severe neurological complications following elective aneurysm surgery or endovascular treatment (72, 78). The risk of an adverse outcome after surgery was importantly affected by patient age while

aneurysm size >12 mm and location of the aneurysm in the posterior circulation were considered important risk factors in patients undergoing endovascular repair (78).

Patients with known unruptured aneurysms who are managed conservatively need to curtail uncontrolled hypertension, smoking, heavy alcohol consumption, stimulant medications, illicit drugs, and excessive straining and Valsalva maneuvers.

2) Extra-Renal Cystic Manifestations: Cysts in the liver, pancreas, lung, spleen, esophagus, ovary, testis, epididymis, prostate, thyroid, bladder, uterus, brain, paraspinal, and seminal vesicle have been described in ADPKD patients (79).

Hepatic cysts: They develop later than renal cysts in ADPKD patients with an increasing prevalence with age (80-82). Women are found to develop larger cysts and at an earlier age which may be related to the sensitivity of cysts to female steroid hormones. An increased frequency of hepatic cysts in postmenopausal women further substantiates this possible relation (80, 81, 83).

Most patients remain asymptomatic with preserved hepatic function. However, patients rarely develop acute pain due to cyst infection or hemorrhage, and rarely from rupture or torsion (82). An infected cyst requires therapy with an antimicrobial such as fluoroquinolone which has good cyst penetration and, in some cases, percutaneous drainage (82). Partial hepatic resection or liver transplantation may be considered in patients with refractory pain or massive symptomatic cysts (82, 84). In non surgical candidates, percutaneous transcatheter hepatic artery embolization may be a treatment option (85).

The immunosuppressive agent, sirolimus (rapamycin) an mTOR inhibitor, appears to decrease polycystic liver volume possibly via its antiproliferative effect on biliary epithelium (86). Data regarding the efficacy of H2-blockers (such as cimetidine or ranitidine) or the somatostatin analogue octreotide in limiting cyst growth is not sufficient enough to support the use of these treatment modalities (87).

Pancreatic cysts: Cysts in the pancreas are a relatively uncommon finding in ADPKD and has been more frequently found with increasing age, female gender and PKD1 form of the disease (88).

Seminal vesicle and ejaculatory duct cysts: They pose a threat to fertility in males and have been linked to sperm abnormalities that include asthenozoospermia, azoospermia, necrospermia and immotile sperms (89, 90). Only detailed studies in the future can warrant if there is a need for basic semen analytic tests, seminal vesicle ultrasound examinations and cryopreservation of sperms at the time of diagnosis.

Arachnoid membrane cysts: They have been found to increase the risk of subdural haematomas (91).

3) Cardiovascular Effect: Valvular abnormalities usually associated with ADPKD patients include mild mitral valve prolapse and aortic regurgitation and less frequently mitral and/or tricuspid regurgitation (92, 93). Most patients are asymptomatic and may require cardiac ultrasonography for confirmation (94). However these lesions may worsen enough over time to require valve replacement (92). Antimicrobial prophylaxis is advised in patients with audible murmurs (60).

Asymptomatic, well tolerated and clinically inconsequential pericardial effusions appear to occur at increased frequency in patients with ADPKD, which may be related to the increased compliance of the parietal pericardium (95).

Studies also suggest an association of ADPKD with an increased incidence of coronary aneurysms, aortic aneurysms and aortic dissections secondary to uncontrolled hypertension (96, 97).

4) Diverticula and Hernias: ADPKD patients on maintainence peritoneal dialysis appear to have an increased risk of colonic diverticula manifested as abdominal pain, diarrhea and heme positive stools and run the risk of colonic perforations (69, 98). They

also appear to be at greater risk of spinal meningeal diverticulas that may present with intracranial hypotension due to cerebrospinal fluid leak (99).

Abdominal wall and inguinal hernias appear with increased frequency in patients with ADPKD, with those treated with continuous ambulatory peritoneal dialysis at an increased risk for an indirect inguinal hernia (100).

5) Other Manifestations: ADPKD patients demonstrate an increased prevalence of radiographic bronchiectasis, which may be attributed to the dysfunction of primary cilia and the primary cilia-related proteins (101).

Ovarian cysts are not usually associated with ADPKD and female fertility is usually not affected by the disease (90, 102).

Diagnosis and Screening

The diagnosis of ADPKD relies primarily on imaging modalities that include ultrasonography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) (103). Ultrasonography remains the most commonly used imaging modality due to cost and safety factors. However its inaccuracy in detecting small cysts or small changes in renal volume may pave way for the use of either CT or MRI (104). MRI is preferred over CT as it avoids exposure to radiation and iodinated contrast media. Nevertheless nephrogenic systemic fibrosis has been linked to the usage of Gadolinium-based MR contrast agents in renal patients and is better avoided in cases with GFR <30ml/min (105, 106). A recent study found un-enhanced MRI technique combined with manual segmentation volumetry to reliably detect and measure the changes in renal volume occurring within a short time interval (107). This can be used to access the progression of disease and the rate of renal function decline.

However genetic testing is made use of in certain settings when a definitive diagnosis is required. The age of the patient, presence or absence of a family history of the disease, family history of other genetic disorders, clinical manifestations of the disease, as well as the number and types of renal cysts are significant details that help in the diagnosis of ADPKD.

Positive Family History

Ultrasonography remains the primary diagnostic modality used in the screening and diagnosis of asymptomatic individuals with a positive family history.

Screening is advisable in all adults [>18yrs] with a positive family history and potential kidney donors. The benefits of screening include knowledge concerning the diagnosis, appropriate family planning, the ability to detect and treat complications associated with the disease, reassurance of unaffected individuals, and appropriate selection of unaffected relatives as possible donors for kidney transplantation. However the adverse consequences of screening that include possible difficulties with insurability, education and employment due to a positive diagnosis, must be taken into consideration especially in children less than 18 years in whom such screening is not recommended. Nevertheless, children at risk for ADPKD should be monitored for early disease presentations that require treatment.

In infants or children less than 18 years of age, the findings of large echogenic kidneys without distinct macroscopic cysts is highly suggestive of the disease. The presence of one cyst is adequate for the diagnosis in an at-risk child (0 to 15 years of age) (108).

Sonographic diagnostic criteria for individuals greater than 15 years of age at 50 percent risk for the disease include the following (109):

-At least two unilateral or bilateral cysts among individuals aged 15 to30 years.

-At least two cysts in each kidney among individuals aged 30 to 59 years.

-At least four cysts in each kidney among individuals

60 years or older.

A negative ultrasound can definitely exclude type 1 disease when the patient is older than 30 years. However, the age when a negative ultrasound excludes type 2 disease is unclear (109, 110). Hence, individuals from families with mid disease may go undiagnosed. This further validates the need of genetic testing in living related donors for patients with polycystic kidney disease, in whom disease status cannot be confirmed with the aid of imaging studies alone (111, 112).

Contrast enhanced CT scanning or MRI or heavy-weighted un-enhanced T2 MR images can reliably detect small cysts of 2 to 3 mm diameter (113). Nevertheless, genetic testing can be used when the imaging results are equivocal and/or when a definite diagnosis is required.

Negative Family History

This refers to cases where the clinical presentation and imaging studies suggest a diagnosis of ADPKD with no relevant family history of the disease. In most such cases, the disease is inherited, but the affected parent has died without a diagnosis or is alive with a mild form of the disease that has gone undetected (52). In the absence of a family history, diagnosis should be strongly suspected in the presence of multiple and bilateral cysts (arbitrarily defined as 10 or more cysts in each kidney) in the absence of findings suggestive of a different renal cystic disease, particularly if renal enlargement or liver cysts are also present.

Differential Diagnosis

The age of the patient, presence or absence of a family history of the disease, family history of other genetic disorders, number and types of renal cysts and the presence of associated manifestations help in the differential diagnosis.

A) Adults and children more than 10 years

Acquired disorders that need to be differentiated from ADPKD include multiple benign simple cysts, localized renal cystic disease, acquired renal cystic disease, medullary sponge kidney and bilateral parapelvic cysts (114). Genetic disorders that should be considered in the absence of a family history of ADPKD include autosomal recessive polycystic kidney disease, autosomal dominant tuberous sclerosis complex, autosomal dominant von Hippel-Lindau disease, autosomal dominant medullary disease, autosomal dominant polycystic liver disease and X-linked dominant orofacialdigital syndrome type I (115).

B) Infants and children less than 10 years

In the absence of a family history of ADPKD, the differential diagnosis of severe presentations in infants or children (up to 10 years of life) include autosomal recessive polycystic kidney disease, Contiguous PKD1-TSC2 contiguous syndrome, Meckel-Gruber syndrome and other multiple malformation syndromes (115, 116).

Genetic Testing

Molecular genetic testing is available for ADPKD and may be useful for evaluation of at-risk individuals with equivocal imaging results, younger at-risk individuals as a living-related kidney donor, and individuals with atypical or de novo renal cystic disease (117). However recent studies indicate that only about 70% of the known pathogenic mutations are identifiable using genotype testing, leaving question marks over its screening efficacy (118). The current methods used to perform genetic testing are linkage or sequence analysis of DNA. Nevertheless, a combined approach using both modalities may be more effective (118).

Prenatal and preimplantation genetic testing: Although prenatal testing is clinically available if the mutation has been identified in an affected family member or if linkage has been established in the family, it is rarely considered for adult-onset conditions such as ADPKD. However it may be carried out in rare families where severe, early-onset disease in one child suggests a significant risk of recurrence of

severe disease in a sibling (94).

Single cell fluorescent PCR is considered a stable and reliable approach for pre-implantation genetic diagnosis (119).

Course of the Disease

Since the diagnosis is often prompted by the onset of symptoms, it is not surprising to find most patients being diagnosed at middle or later ages, unless of course they are screened early due to a positive family history of the disease. Although ADPKD may lead to end stage renal disease [ESRD] very early in life, progression to ESRD most frequently happens in middle age and later (3, 120).

The decline in renal function with time has been assumed to be due to the pressure exerted by enlarging cysts on the normal renal parenchyma. Histologic evidences correlate the progressive renal failure in ADPKD most closely with the development of vascular sclerosis and interstitial fibrosis (58). Apoptosis (programmed cell death) induced in non-cystic glomerular and tubular cells by existing cysts may also play an important role (121).

Causes of death in ADPKD seems similar to patients with other causes of end-stage renal disease, with most deaths attributable to cardiac causes followed by infections and neurological causes (ruptured intracranial aneurysm or hypertensive intracerebral hemorrhage) (122).

Progressive renal disease in ADPKD patients is associated with certain risk factors that include:

Younger age at diagnosis: Patients diagnosed an earlier age have a worse prognosis unless found as a result of asymptomatic family screening (123).

Male sex: The male gender is usually associated with an accelerated progression of renal disease particularly in PKD 1 patients (124). Elevated levels of testosterone were linked to increased cyst growth in murine models of the disease (125).

Genetic variations: The occurrence of cysts and end-stage renal disease are delayed in PKD2 disease (mean age 74.0 as against 54.3 years in PKD1) (8, 9). This genetic heterogeneity accounts for interfamilial variability. It has been suggested that the prognosis in a given patient could be inferred from the course of other family members (126). However intrafamilial variability is often linked to the occurrence of a somatic mutation in the intact allele within epithelial tubular cells '2nd hit hypothesis' (8, 11, 12).

Kidney growth rate: Faster rate of growth in kidney and cyst volumes is directly associated with a faster rate of decline in glomerular filtration rate (GFR) (127). At any given age, kidney volume growth is assumedly the best marker, predicting the subsequent rate of progression and the risk of renal insufficiency (38).

Hypertension (onset before age of 35 years): Uncontrolled and early onset hypertension has been associated with faster progression of renal disease (123).

Gross hematuria (1st episode before 30 years): Gross hematuria is more likely among individuals with larger kidneys, hypertension and higher plasma creatinine concentrations (50) and may reflect accelerated cyst expansion and rapid progression of kidney disease in ADPKD.

Other risk factors include black race, hyperlipidaemia, low HDL cholesterol concentrations, and sickle cell trait (123).

Pregnancy: Hypertensive women have an increased risk for fetal loss, preeclampsia and perinatal mortality and needs careful monitoring (128). In contrast normotensive women with normal renal function usually have successful, uncomplicated pregnancies (129). However, those women who develop new-onset hypertension are more likely to develop chronic hypertension (129). There is also an increased risk of ectopic pregnancy in ADPKD females (129).

Novel therapies in ADPKD

1) Inhibition of Cyst Fluid Secretion: Various therapeutic strategies are being designed to slow

cyst growth and enlargement in autosomal dominant polycystic kidney disease of which vasopressin V2 receptor antagonists provide the best hope for an effective therapy.

Vasopressin receptor antagonists: Vasopressin is the major adenylyl cyclase agonist in the collecting duct principal cells acting via V2 receptors. The arginine vasopressin V2 receptor antagonists OPC-31260 and Tolvaptan (OPC-41061) were found to lower renal cAMP levels and decrease the severity of cyst formation in PCK mice and in three other animal models which are orthologous to human diseases [autosomal recessive polycystic kidney disease (PCK rat), autosomal dominant polycystic kidney disease (Pkd2-/WS25 mice), and nephronophthisis(pcy mouse)] (130-132).

It is also notable that PCK rats which were homozygous for an arginine vasopressin mutation and did not express vasopressin were completely protected from renal cyst formation (133). Administration of V2 receptor agonist 1-deamino-8-D-arginine vasopressin to these animals induced cyst genesis (133, 134).

Phase III trials on tolvaptan are being organized in polycystic kidney disease, with phase II trials indicating the drug to be safe and well tolerated in autosomal dominant polycystic kidney disease (135).

Other approaches:

a) Amiloride: Potassium-sparing diuretic amiloride by blocking sodium channels was found to inhibit cyst development in animal models of the cystic disease (136). Amiloride has also been shown in vitro to diminish sodium transport in human low-sodium cysts (137).

b) Somatostatin: Somatostatin analogues have shown to reduce cystic fluid secretion mediated via active chloride transport whereby decreasing renal cyst progression in patients with ADPKD (138).

c) Caffeine restriction: Caffeine acts by increasing cyclic AMP levels and has shown to promote cyst growth in invitro studies (139).

2) Inhibition of Cyst Epithelial Proliferation: Various medical intervention studies on murine models have suggested a decrease in cystic disease progression some of which have not yet been tested in the clinical setting, others are the object of ongoing studies.

a) Sirolimus: Sirolimus (rapamycin) an mTOR inhibitor was found to inhibit cyst formation and decrease polycystic kidney size in several animal models (140). Sirolimus and Everolimus (another mTOR inhibitor) are under phase 2 clinical trials (141).

b) Caspase inhibitors: They have shown to reduce tubular apoptosis and proliferation and renal failure in murine models of the cystic disease (142).

c) Microtubule specific taxanes: Paclitaxel (taxol) in particular was found to inhibit progression of cystic disease in PCK mice (143).

d) Statins: Animal models treated with lorvastatin showed an improvement in renal function (144). Simvastatin treatment was found to ameliorate renal function in ADPKD patients and brought about an improvement in endothelial dysfunction in them (145).

e) Urinary alkanization: A reduction in ammonia genesis with alkali therapy was found to reduce the severity of the cystic disease and interstitial inflammation in a rat model of the cystic disease (146).

f) Methylprednisolone: Methylprednisolone was found to decrease the extent of renal enlargement and renal interstitial fibrosis in mice and rats with relatively severe forms of inherited polycystic kidney disease (147).

Other therapeutic approaches which were found to ameliorate the severity of cystic kidney disease in murine models include inhibitors of Erb-B1 (epidermal growth factor receptor)and Erb-B2 tyrosine kinase, mitogen-activated protein kinase inhibitors, peroxisome proliferator-activated receptor agonists,

antisense C-myc oligonucleotides and cyclin-dependent kinase inhibitors (148-151).

3) Control of Hypertension: Angiotensin converting enzyme (ACE) inhibitors can effectively lower blood pressure in most ADPKD patients. Recent studies have failed to detect a beneficial effect of ACE inhibition on loss of renal function in ADPKD patients (152, 153). However its potential protective effect on left ventricular hypertrophy helps decrease reduce left ventricular myocardial infarction, thereby preventing cardiovascular morbidity and mortality (154).

Angiotensin II blocker candesartan has a beneficial effect on reducing urinary liver-type fatty acid-binding protein (L-FABP) levels which was found to be significantly higher in ADPKD patients (44). Free fatty acids (FFAs) bound to albumin gets overloaded in renal proximal tubules and exacerbate tubulointerstitial damage (44). An ongoing study (HALT-PKD) has been designed to study the efficacy of a combination therapy with ACE inhibitors and angiotensin II receptor blockers (155). The optimum blood pressure target is also uncertain and the effectiveness of a tight blood pressure control is being evaluated in an ongoing clinical study (156).

Patients who are intolerant to ACE inhibitors may shift to angiotensin receptor blockers. Women in child-bearing years should be counseled about the potential risks of ACE inhibitors and ARBs, and may switch to alternate antihypertensive drugs prior to planned pregnancy. Patients who develop a clinically significant elevation in the plasma creatinine concentration may be more safely treated with another agent, such as a calcium channel blocker.

Renal denervation was found to be efficacious in reducing hypertension in a rat model of the cystic disease indicating renal innervations to be major contributors to hypertension pathogenesis (45).

4) Dietary Protein: The efficacy of dietary protein restriction on progression of autosomal dominant polycystic kidney disease remains inconclusive (64).

5) Cyst Drainage: Percutaneous aspiration, aspiration with sclerosis and surgical drainage have been effectively used in patients to relieve intractable pain and discomfort caused by the enlarging cysts. These measures have however not proved to improve renal function or delay the rate of disease progression (64).

Percutaneous aspiration with or without sclerosing agents have been associated with high rate of recurrence (157). However aspiration should be considered in the drainage of small symptomatic cysts upto 6cm in diameter (158). Retroperitoneal laparoscopic cyst decortication has been the preferred treatment modality of late, this being a safe, effective and minimally invasive alternative to open surgery in symptomatic renal cysts (159). However robotic surgery may be preferred to decorticate peri-pelvic cysts around the renal hilum (160).

6) Renal Denervation and Nephropexy: Laproscopic renal denervation and nephropexy was found to be an effective and promising option for uncontrolled ADPKD related pain in children and adolescents (161). However its long term durability and effectiveness is yet to be established.

7) Transcatheter Arterial Embolization (TAE): TAE being less invasive than surgery is a safe and effective therapeutical option for ADPKD patients with massively enlarged kidneys and those with haemorrhage into cysts. A retroperitoneal or subcapsular heamatoma that may lend haemodynamic instability may also be benefited by embolization. TAE has shown to improve the quality of life and nutritional status of patients with ADPKD (162).

8) Renal Replacement Therapy: ADPKD patients who progress to end-stage renal disease may require renal replacement therapy in the form of either dialysis (hemo/peritoneal) or renal transplantation.

a) Hemodialysis: Survival of ADPKD patients undergoing hemodialysis appears to be superior to of patients with other causes of end-stage renal

disease (163). This could be accounted for by a lower incidence of coronary artery disease in these generally more healthy patients with ADPKD (164). However ADPKD patients undergoing hemodialysis were more prone to have renal pain, gross hematuria, and renal infection (163).

b) Peritoneal dialysis: Patients with polycystic kidney disease had an adjusted survival benefit associated with peritoneal dialysis, compared to patients with other causes of renal disease (165). However, repeated peritoneal dialysis has been associated with an increased risk for peritonitis (166). This form of therapy requires adequate intra abdominal space for effective peritoneal exchange and is hence not advisable in ADPKD patients with markedly enlarged kidneys or recurrent hernias (167).

c) Renal transplantation: The overall patient and graft survival rates did not differ between ADPKD patients and those in whom transplantation was indicated for other reasons (168). However, the potential need for nephrectomy is specific for ADPKD patients. Earlier studies suggested a few complications to be specific for ADPKD patients that include post-transplant erythrocytosis, symptomatic aneurysms, urinary tract infections, diverticulitis, and gastrointestinal disorders requiring surgery (169-171). Studies of late have refuted these observations and have found no complication to occur more frequently in ADPKD patients (168, 172).

d) Nephrectomy: Growing cysts increase renal size to enormous proportions over time and may lead to chronic pain, chronic haematuria, recurrent urinary tract infections, abdominal hernias and marked fatigue and anorexia due to pressure on intraabdominal organs most of which may be relieved by unilateral or bilateral nephrectomy(173, 174).

Nephrectomy may also be considered to accommodate the allograft better and can be performed pre-, during or post-renal transplantation (173, 174).

Nephrectomy prior to renal transplantation is advisable in the presence of recurrent infection, suspected malignancy, or extension of the native polycystic kidney into the potential pelvic surgical site. The overall patient and graft survival rates appear to be similar for the concomitant and post-transplant nephrectomies, with concomitant nephrectomy and transplantation yielding increased patient satisfaction (173). However blood loss, operative time and hospitalization length are greater for concomitant nephrectomies (175).

The once preferred open nephrectomy has been replaced by minimally invasive laproscopic or robot assisted approaches as the technique of choice. Compared to open surgery, the laparoscopic approach results in significantly shorter hospital stay, decreased morbidity and blood loss, quicker recovery and excellent cosmesis (176).

Conflict of Interest

None declared.

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