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AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE AND NEW TREATMENT APPROACHES

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ABSTRACT

Autosomal dominant polycystic kidney disease is the most common inherited kidney disease, results in progressive loss of renal function due to the development and growth of cysts. Advances in understanding the nature of the disease have led to increased awareness of ADPKD, improvements in imaging modalities for diagnosis and assessment and the availability of effective therapies because patients with ADPKD often experience a range of renal and extrarenal complications. Approximately 78% of cases of ADPKD arise from PKD1 mutations. PKD2 mutations account for another 15%. These mutation-driven changes produce the hallmark disease process of ADPKD: development of large, fluid-filled cysts in the kidney, which over time increase kidney size and volume and compromise kidney function, leading to decreased life expectancy, need for dialysis and/or transplantation, cardiovascular/cerebro-vascular disease, and intracranial aneurysms. The involvement of the vasopressin system makes it a target for therapy designed to slow progression of ADPKD. Steps are to taken to slow down the progression of disease by early diagnosis and symptomatic treatment approaches are needed to be followed to prevent the complications. As RAAS mechanisms are prime factors for progression and worsening of the condition, steps should be taken to prevent the over activity of RAAS by using many of the newer therapeutic agents show promise in preventing or stabilizing cyst growth, providing much needed hope in this currently relentless condition. Hypertension should be kept in check to prevent any chances of strokes. Making lifestyle changes such as dash diet and maintaining adequate hydration to maintain the normal renal sufficiency are some of the key approaches to control or to prevent the progression of this condition and help the patient to lead normal life and life expectancy.

KEYWORDS: Autosomal dominant polycystic kidney disease, Treatment of ADPKD, Progression.

INTRODUCTION

Autosomal dominant polycystic kidney disease(ADPKD) is an inherited, systemic disorder characterized by a progressive increase of bilateral renal cysts, leading to chronic kidney disease (CKD) and—in about 70% of cases at a median age of 58 years—end-stage kidney disease (ESKD).[1] One-half of people with ADPKD will require dialysis or kidney transplantation by the age of about 60 years.[2] About 6 million people worldwide have ADPKD. Most cases of the disease arise from mutations to 2 major genes, PKD1 (chromosome 16.p13.3, ~78%) and PKD2 (4p21, ~15%); other involved genes include GANAB (11q12.3), which was recently discovered.[2-5] Family history indicates genetic inheritance in 90% of patients, but 10% of patients have no known family history due to the possibility of de novo mutations, mosaicism, mild disease from PKD2, nontruncating PKD1 mutations, or unavailability of medical records.[5] ADPKD is classified as a ciliopathy because PKD mutations lead to protein expression localized to the primary cilia of tubular epithelial cells.[2] Disruptions in these cells in vasopressin-sensitive distal nephrons and collecting ducts lead to enhanced proliferation, increased fluid secretion, expression of inflammatory cytokines, and destruction of renal parenchyma.[4] These mutation-driven changes produce the hallmark disease process of ADPKD: development of large, fluid-filled cysts in the kidney, which over time increase kidney size and volume and compromise kidney function, leading to decreased life expectancy, need for dialysis and/or transplantation, cardiovascular/cerebrovascular disease, and intracranial

aneurysms.[1,2,6] The involvement of the vasopressin system makes it a target for therapy designed to slow progression of ADPKD.

Stages of Adpkd

ADPKD often progresses for many years without causing symptoms, but the cyst burden and the total kidney volume (TKV) inexorably increase with age.[7-9]

S. No:	STAGE	DESCRIPTION
1	SUBCLINICAL	Gene carriers, few small cysts, normal blood pressure, normal kidney function (>90 mL/min/1.73 m2 or age-appropriate for child). Few or no symptoms.
2	EARLY STAGE	Kidneys are enlarged with multiple cysts, but structural integrity preserved, hypertension present, well-maintained kidney function (>60 mL/min/1.73 m^2). Impaired concentrating ability may be present. Appearance of complications such as cyst hemorrhage, infection, or nephrolithiasis may occur.
3	LATE STAGE	Multiple cysts, enlarged kidneys, hypertension present, moderate renal insufficiency (<60 mL/min/1.73 m2). Complications related to large kidney volume including cyst hemorrhage, infection, or nephrolithiasis and abdominal distention and discomfort occur more commonly. Possible hepatomegaly and hepatic cyst complications may occur.
4	ADVANCED	Multiple cysts, substantially enlarged and distorted kidneys, with little preserved parenchyma; hypertension present; severe renal insufficiency (<30 mL/min/1.73 m2). Complications related to large kidney volume including cyst hemorrhage, infection, or nephrolithiasis and abdominal distention and discomfort occur more commonly. Abnormal distension from enlarged kidneys.

Subclinical features such as small cysts may be detected in children and infants.[10] A family history of ADPKD should raise the index of suspicion, leading to vigilant monitoring for the disease. In adolescents, the kidneys may be enlarged and multiple cysts may be present, but their structure and function remain intact (ie, glomerular filtration rate [GFR] >60 mL/min/1.73 m2). Hypertension is usually present; other potential complications include cyst hemorrhage, cyst infection, and kidney stones.

Diagnosis

Typically, ADKPD is diagnosed in the later stage, in adults who may present with a range of complaints including renal insufficiency (GFR <60 mL/min/1.73 m2), flank pain, abdominal distention and fullness, hematuria, urinary tract infection, hypertension, and kidney stones.[Bergmann 2018] Advanced ADPKD involves substantially enlarged and distorted kidneys with little preserved parenchyma and advanced kidney insufficiency (GFR <30 mL/min/1.73 m2). Extrarenal complications, such as brain aneurysms and cysts in other organs (eg, pancreas, liver, prostate), are common in ADPKD and may be life-threatening Family history of ADPKD leads to diagnosis in about half of cases. About one-third of cases are diagnosed because the patient reports signs or symptoms, and the rest because an alert clinician observes signs or characteristic abnormalities.[14] Over time, as cysts form and increase in size and number, TKV increases and the GFR declines. However, reductions in nephron mass may be masked by compensatory changes in GFR.[3] As a consequence, GFR values may appear normal for several years, until compensation ultimately fails and GFR declines steeply. By the time the decline in GFR is detected, the kidneys have already been significantly damaged. Ideally, subclinical physiological changes are detected early in the disease process so that patients can be referred to a nephrologist early on—and treatment for ADKPD can be initiated—before the kidneys develop significant and irreversible damage.

Approximately 78% of cases of ADPKD arise from PKD1 mutations. PKD2 mutations account for another 15%. Other mutations (GANAB, DNAJB11, etc) have also been found to be involved in rare cases. Truncating mutations are associated with more severe kidney disease compared to nontruncating mutations. Patients with PKD2 mutations have milder kidney disease with fewer renal cysts, delayed onset of hypertension and ESRD, and longer survival.[18] Another tool for predicting renal survival is the Predicting Renal Outcomes in ADPKD (PROPKD) score (Table 1), derived from a study of 1341 patients from 913 pedigrees who had ADPKD of known genotype.[19] Points are assigned based on the presence or absence of various risk factors (gender, hypertension, and urologic complications in patients <35 years of age) and type of genetic mutation. A score of >6

forecasts the onset of ESKD before age 60 years (positive predictive value [PPV] 90.9%).

Table 1: Ultrasound Criteria for Diagnosis of ADPKD.[16,20]

Variable	Category	Points
Gender	Female	0
	Male	1
Hypertension with age < 35 years	No	0
	Yes	2
At least 1 urological complication age <35 yrs	No	0
	Yes	2
Mutation	PKD2	0
	PKD1/Non-truncating	2
	PKD1/Truncating	4
Total		0 to 9 points

Ultrasound is the most commonly used modality for the diagnosis of ADPKD.[21] The Pei criteria define the number and location of renal cysts (unilateral or bilateral) according to the patient's age (Table 2). Use of these criteria for diagnosis has demonstrated high PPV and specificity for ADPKD in patients with either the PKD1 or PKD2 mutations (except for younger patients with a family history of PKD2 disease).[20] As imaging technology continues to improve, so do the criteria for diagnosis. A 2018 study found that high-resolution ultrasound may be as accurate as MRI.[22]

Table 2: Ultrasound Criteria for Diagnosis of ADPKD.[16,20]

Age (yrs)	No. of cysts required for diagnosis
15—39	Total >3
40—59	Unilateral or bilateral
≥60	Total >4

MRI may be more sensitive and superior for diagnosis and monitoring. Pei criteria for MRI state that in patients between the ages of 16 and 40 years with a positive family history, the presence of more than 10 cysts is diagnostic for ADPKD, while a finding of fewer than 10 excludes the diagnosis.[Pei 2015] If results of ultrasonography are uncertain, MRI may clarify the diagnosis. MRI is superior to ultrasound for excluding a diagnosis of ADPKD.[23] Computed tomography has not been validated for diagnosis of ADPKD. There is a high rate of false-positive results because renal cysts are prevalent among the general population.[24] If CT is used and if simple cysts larger than 1 cm are detected, the criteria for ultrasound diagnosis apply.[20] Each imaging modality has its strengths and limitations.[25] Ultrasound detects cysts 10 mm or greater in diameter, although new high-definition ultrasound techniques can detect cysts as small as 2 mm to 3 mm; MRI and CT can detect cysts >2 mm. Ultrasound does not involve radiation, is noninvasive, is widely available, and costs less than other modalities. However, results are highly dependent on the skill of the operator and are less precise for detecting changes in TKV in the short term. CT accurately measures TKV and cyst volume and can be used in patients who have metallic implants such as pacemakers, but it exposes the patient to radiation, and the contrast medium, if needed, is potentially nephrotoxic.[25] MRI is also accurate for TKV assessment, and it allows quantitative assessment of disease by allowing segmentation of individual cysts with low interoperator variability; there is no exposure to radiation and it may be better for small renal lesions, especially those >2 mm in diameter. Cost and availability may limit its use though. Unless the initial evaluation suggests a condition that is better characterized on CT scan than sonography, ultrasound would be the preferred first-line choice for imaging.

Treatment Approaches

Although ADPKD will inevitably progress over time, effective strategies are available to slow its progression in many patients. In April 2018, the landscape changed when tolvaptan, a vasopressin V2 receptor antagonist, became the first drug therapy approved for use in adults at risk for rapidly progressing ADPKD. Clinicians now have many tools to design a comprehensive plan to manage the factors that contribute to progression—as well as the potential complications of the disease—and to improve outcomes for their patients with ADPKD. Activation of the renin-angiotensin-aldosterone system (RAAS) is a key aspect of the pathophysiology of ADPKD. RAAS inhibitors thus form the cornerstone of antihypertensive therapy. Monotherapy with either an ACE inhibitor or an ARB is considered the first-line approach. Combination therapy with an ACE inhibitor and an ARB has not been found to provide additional benefit. CCBs and thiazide diuretics may be considered as a second-line options for ADPKD patients, especially those with resistant hypertension.[15,29,30] A crucial first step is to address hypertension, which is one of the earliest signs of ADPKD and which can develop in up to 70% of patients even before the decline in renal function is detected.[31,32] Hypertension can appear in patients at any age, including children; the average age of onset of hypertension associated with ADPKD is about 30 years.[33] Evidence suggests that the development and

expansion of cysts upregulates the intrarenal RAAS, resulting in the destruction of cilia, reduction in local blood flow, loss of polycystin-1 and, ultimately, hypertension, which increases the risk of serious cardiovascular and cerebrovascular complications such as left ventricular hypertrophy, valvular abnormalities, myocardial infarction, stroke, and rupture of intracranial aneurysms.[1,16,34]

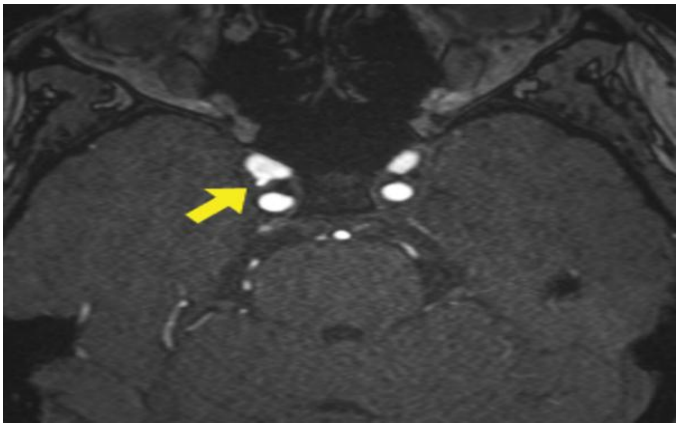

Fig. 1: Small berry aneurysm of the internal carotid artery, as seen on axial 3-dimensional magnetic resonance angiography (MRA).

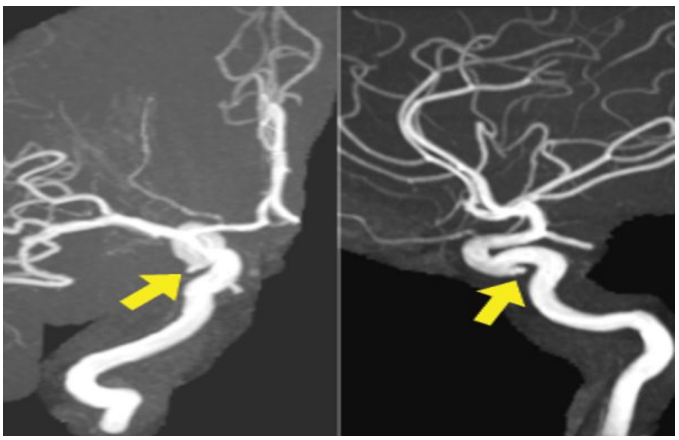

Fig. 2: Small berry aneurysm is better seen on projection images, where the 3-dimensional data can be rotated.

The prevalence of intracranial aneurysm (ICA) in ADPKD may be as high as 12%, compared with <3% in the general population.[23,35] The prevalence is higher in patients who have a first-degree relative with a history of ICA (up to 20%). The most serious complication of ICA is subarachnoid or intracerebral bleeding. Rupture occurs a decade earlier compared with patients with sporadic ICA. Rupture of ICA can be fatal in about half of the cases. Screening for ICA, usually with MRA, is a reasonable approach, especially in the context of family history of aneurysm/subarachnoid hemorrhage, history of hypertension, history of smoking, or personal history of intracranial hemorrhage. Repeat screening every 5 years should be considered after a negative initial study. As outlined by the Kidney Disease: Improving Global Outcomes (KDIGO) expert panel, strict blood pressure control is essential for patients with polycystic kidney disease (PKD).[8] A key first step is to reduce sodium intake. Clinicians should be prepared to counsel patients—or refer them for counseling—about nonpharmacologic strategies for lowering sodium intake. The Dietary Approaches to Stop Hypertension (DASH) trial found that restricting sodium intake (eg, to <2300 mg/day) can significantly reduce systolic blood pressure.[36] Further dietary strategies are discussed below. The randomized HALT-PKD study (N=558 patients aged 15-49) was designed to compare the effects of treating to a standard blood pressure target (120/70 mm Hg to 130/80 mm Hg) or to a low target (95/60 mm Hg to 110/75 mm Hg) in patients with ADPKD.[30] The primary outcome was annual percentage change in TKV. Therapies included lisinopril (an ACE inhibitor [ACEi] + telmisartan, an angiotensin receptor blocker [ARB], and lisinopril + placebo. Rigorous blood pressure control attenuated the annual rate of increase in TKV by 14.2%. Other results included no overall change in eGFR, a greater decline in the left ventricular mass index, and greater reduction in urinary albumin excretion. The use of combination therapy was not shown to convey additional benefit compared to monotherapy with lisinopril.[30] The key takeaway is that monotherapy with an ACEi or an ARB is considered to be the first-line therapy for patients with ADPKD and hypertension.[15] In addition, in younger PKD patients, the target for blood pressure control should be much lower than the standard target (ie, 95/60 mm Hg to 110/75 mm Hg). Chronic pain

is a common feature of ADPKD, occurring in perhaps 60% of cases, and is often severe enough to interfere with activities of daily living.[27] Abdominal, flank, or back pain can result from pressure of the enlarged kidneys on neighboring organs and tissues. Acute pain may result from cyst rupture, infection, hemorrhage, or nephrolithiasis.[8,11] Managing pain effectively can be challenging in these patients. Nonopioid analgesics such as acetaminophen, clonidine, and tramadol may be considered.[22] Use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and cyclo-oxygenase-2 (COX-2) inhibitors, is not recommended because of their adverse effects on the kidneys, especially in patients on RAAS-blocking agents or with an eGFR <50 cc/min.[11] These drugs act by blocking prostaglandins, leading to decreased blood flow and loss of renal function.[1] For moderate to severe pain, opioids may be an option but the doses should be modified based on the patient's eGFR.[22] Other supportive measures include heating pads, support garments, nerve stimulation, and physical therapy. More aggressive interventions for disabling pain involve invasive procedures to reduce or remove cysts. Referral to pain management team, if available, can be helpful for managing chronic pain in patients with ADPKD. Hydration with water may help slow the progression of ADPKD, but evidence is lacking or contradictory.[22] Clinical trials are under way to evaluate this approach. In the meantime, a reasonable strategy calls for moderately enhanced fluid intake, mostly water, spread out over 24 hours. Typically, patients who adhere to diets that restrict sodium and protein intake have lower osmolar loads and need to drink less water. Evidence is inconclusive to suggest that the use of lipid-lowering statin drugs may provide benefit in patients with ADPKD. One randomized, double-blind, placebo-controlled phase 3 clinical trial looking at the effects of pravastatin on htTKV and left ventricular mass index by MRI found that the drug was effective in slowing the progression of structural kidney disease in older children and young adults with ADPKD.[37] However, a post hoc analysis of the HALT-PKD trial found no difference between patients who had never used statins and those who had used them for at least 3 years on outcomes including percentage change in TKV or change in eGFR.[39] Statins should be considered in patients with reduced eGFR who are at risk for developing cardiovascular complications. Studies are under way to evaluate potential benefits from use of statins in patients with ADPKD.[38-41]

Slowing Disease Progression

Patients with ADPKD overexpress vasopressin, which upregulates cyclic adenosine monophosphate (cAMP), resulting in impaired urine-concentrating ability and increased formation and growth of cysts.[42] Inhibiting the V2 receptor thus helps control disease progression. In 2018, tolvaptan, a novel selective vasopressin V2 receptor antagonist, became the first US Food and Drug Administration (FDA)-approved drug indicated for adults with ADKPD who are at high risk for progression. As noted above, factors that increase risk include age <45 years with a kidney length >16.5 cm; mainly large kidneys in young PKD patients; male sex; PROPKD score >6 (eg, truncating PKD1 mutation); early onset of clinical symptoms such as hematuria/cyst rupture and/or infection; family history of ESKD before the age of 58; and overt proteinuria and macroalbuminuria.[1] The efficacy of tolvaptan was demonstrated in 2 pivotal trials, TEMPO and REPRISE.[43,44] In the 3-year, phase 3 TEMPO trial (N=1445), the rate of increase in TKV for the tolvaptan group was 2.8% per year vs 5.5% per year for the placebo group (P<.001).[44] Tolvaptan also yielded significantly lower rates of kidney pain along with a slower decline in kidney function. Adverse events associated with tolvaptan included thirst, polyuria, nocturia, urinary frequency, polydipsia, renal pain, hematuria, and abnormalities in liver function testing. In the 12-month, phase 3 REPRISE trial (N=1370), there was a significant difference in change from baseline in eGFR with tolvaptan treatment (P<.001). This finding indicated a delay in decline of renal function with tolvaptan vs placebo.[44] Pending updated guidelines that incorporate emerging data on the role of tolvaptan in clinical practice, expert consensus and clinical experience continue to refine the approach to use of the drug. The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommends tolvaptan for adult ADPKD patients aged <50 years with an eGFR of >45 mL/min/1.73 m^2 who have demonstrated or who are likely to have rapidly progressing disease.[1] The ERA-EDTA also recommends not starting tolvaptan in patients aged 30 to 40 years with an eGFR of >90 mL/min/1.73 m^2 or those aged 40 to 50 years with an eGFR of >60 mL/min/1.73 m^2. Patients up to age 65 years—especially males—may be considered for treatment depending on circumstances. The drug is not approved for patients <18 years, but a clinical trial is under way involving adolescents between the ages of 12 and 17 years.[45] Patients also must be monitored for their ability to tolerate the drug. In about half of cases, use of vasopressin antagonists can limit water reabsorption, leading to aquaresis-associated adverse effects such as polyuria, thirst, and polydipsia, which may have a significant impact on patients' quality of life.[47] Patients often must limit their activities because of the constant need for access to toilets. Nocturia—frequent awakenings to use the bathroom—may lead to excessive daytime fatigue and sleepiness. To increase their tolerance for the drug, patients should be queried about their current fluid intake and nighttime voiding patterns, assessed for hyponatremia or hypernatremia, and counseled on strategies for appropriate fluid intake including avoidance of alcohol, caffeine, and some citrus juices (such as grapefruit), which may interfere with drug metabolism.[15] On the Horizon: Future Therapeutic Options for ADPKD Novel molecules are being evaluated for their potential role in managing PKD. Among the potential candidates are the somatostatin analogues, which can inhibit cAMP signaling. In a study of lanreotide, patients with polycystic liver disease had a

4% reduction in cyst volume after a year of treatment.[49] A long-term (3-year) study on octreotide in patients with severe ADPKD found no effect on the rate of eGFR decline but slower increases in htTKV.[50] A molecule in the same class as tolvaptan, lixivaptan, is in clinical trials.[15] This drug may offer greater selectivity for target vasopressin receptors with a potential for a lower risk for adverse effects. Tesevatinib, a tyrosine kinase inhibitor, was shown in nonclinical studies to reduce proliferation of renal ductal epithelial cells and thus prevent cyst formation.[16] Tesevatinib is in clinical trials for ADPKD.[51] Other drugs of interest in the clinical pipeline include: Bardoxolone, Glucosylceramide synthase inhibitors, Metformin, Nicotinamide, Pioglitazone

CONCLUSION

Autosomal dominant polycystic kidney disease is one of the most common inheritable conditions. With an incidence 10 times that of sickle cell disease and 15 times that of cystic fibrosis, effective treatment options for ADPKD are widely sought, but remain an elusive goalSteps are to taken to slow down the progression of disease by early diagnosis and symptomatic treatment approaches are needed to be followed to prevent the complications. As RAAS mechanisms are prime factors for progression and worsening of the condition, steps should be taken to prevent the over activity of RAAS by using many of the newer therapeutic agents show promise in preventing or stabilizing cyst growth, providing much needed hope in this currently relentless condition. Hypertension should be kept in check to prevent any chances of strokes. Making lifestyle changes such as dash diet and maintaining adequate hydration to main the normal renal sufficiency are some of the key approaches to control or to prevent the progression of this condition and help the patient to lead normal life and life expectancy.

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