Recognition and Management of a Less Common Cause of Chronic Kidney Disease: Autosomal Dominant Polycystic Kidney Disease

Matthew Weir, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this review article on ADPKD, participants should be able to:

- **Identify** people at high risk for ADPKD
- **Conduct** a diagnostic evaluation
- **Initiate** evidence-based therapy to slow kidney progression and treat extra-renal manifestations

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of chronic kidney disease.

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FACULTY

Matthew R. Weir, MD, Director of the Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder with an incidence of 1 in 1000 live births in the United States.[1] The progressive development and enlargement of renal cysts results in an exponential increase in total kidney volume. Some polycystic kidneys grow to be as large as a football and weigh as much as 30 pounds. Despite destruction of renal parenchyma, normal renal function usually is maintained for decades because of compensatory hyperfiltration in surviving glomeruli. However, when the majority of nephrons have been destroyed, typically during the fourth decade of life, renal function begins to decline, often leading to end-stage kidney disease (ESKD).[2] This is in sharp contrast to the much rarer autosomal recessive form of polycystic kidney disease that often is apparent at birth or in early infancy, frequently leading to death early in life.[1]

ADPKD is caused by mutations in the *PKD1* and *PKD2*

genes. These genes provide instructions for making proteins thought to be involved in normal kidney development, organization, and function.[1] Approximately 90% of individuals with ADPKD inherit a *PKD1* or *PKD2* mutation from 1 affected parent. The other 10% of cases are acquired, resulting from a new mutation in 1 of the genes in people with no family history of the disorder.[1] Historic evidence indicates that the *PKD1* mutation occurs in 85% of people with ADPKD and the *PKD2* mutation in 15%. Recent evidence in individuals from Canada and the United States suggests that the prevalence of *PKD2* could be approximately 30%.[3]

Variants in other genes linked to PKD, as well as environmental factors such as acute kidney injury, can influence cyst formation and disease progression.[4] Compared with *PKD2*, *PKD1* mutation is associated with greater cyst number and volume at a given age and results in more severe disease.[5] People with the *PKD2* genetic mutation generally experience milder kidney disease with fewer kidney cysts, delayed onset of hypertension and ESKD by nearly 2 decades, and longer overall survival.[6-8] However, because the renal prognosis differs according to the type of mutation in both *PKD1* and *PKD2,* the renal prognosis of patients with a *PKD2* mutation is not always favorable compared with patients with a *PKD1* mutation.[6]

DIAGNOSIS

Case scenario

A family physician sees a 28-year-old female for a preventive health visit. She appears healthy. Vital signs: BP 146/92 mm Hg (132/78 mm Hg 6 years ago); HR 74/min; RR 15/min; T 36.8°C. Her liver appears slightly enlarged. She reports that her belly generally feels full.

The diagnosis of ADPKD typically occurs in common clinical settings, such as routine evaluation in an asymptomatic patient with a positive family history of ADPKD, incidental finding during an imaging study conducted for pregnancy, trauma, surgery, or some other unrelated reason, initial evaluation for hypertension, or evaluation for hematuria, cyst rupture, kidney stones, or some other potential symptom related to ADPKD. Consideration should be given to non-ADPKD causes of hematuria and back pain, such as cancer, particularly in patients age >50. Asymptomatic at-risk people usually are not screened until adulthood because there is a lack of disease-specific treatment for this group. However, in children and adolescents, recent guidelines recommend ongoing surveillance or immediate diagnostic screening in those who are asymptomatic but at risk of ADPKD.[9]

Because 90% of patients with ADPKD have a genetic cause, obtaining a detailed family history is the first step in the diagnostic evaluation. The family history should elicit the number and relationship of affected family members, age at diagnosis, age at ESKD development, and known genetic mutations. If the family history is positive, diagnosis is confirmed primarily through imaging.[2,4] For those without a family history of ADPKD, the history should elicit information to assess the presence of other acquired disorders such as multiple benign simple cysts, autosomal dominant tuberous sclerosis complex, and von Hippel-Landau disease.

Imaging with ultrasound generally is used first because of its low cost and widespread availability, but is less sensitive than magnetic resonance imaging (MRI) or computed tomography (CT). If the ultrasound is positive, MRI or CT is appropriate and more useful for determining prognosis. If MRI or CT is positive for ADPKD, referral to a nephrologist is recommended. Imaging might not be definitive in those with manifestations of mild disease such as low cyst size and/or burden (not unusual in some children with ADPKD), in which case genetic testing could be helpful. Otherwise, genetic testing often is limited to patients with atypical presentation, the presence of a few cysts but negative family history, or to rule out ADPKD in a young potential kidney donor.[2,4,10,11]

The diagnostic evaluation should assess for complications. Some involve the kidneys and urinary tract, such as gross hematuria in one-third of individuals, recurrent urinary tract infections in 30% to 50%, and kidney stones in 10% to 35%.[12] Beyond the kidneys, cysts often occur in the liver and less commonly in the pancreas, seminal vesicles, and arachnoid membrane.[4] Cardiovascular disorders often occur, including hypertension, heart valve abnormalities, and aortic and intracranial aneurysms.[13] Arterial hypertension occurs in approximately 50% to 70% of individuals when kidney function is still normal and might be the presenting sign.[13,14] Metabolic complications include insulin resistance and dyslipidemia.[15]

PROGNOSIS

Once an ADPKD diagnosis has been established, a key step is to identify individuals who are at high risk of progressing to chronic kidney disease because this informs prognosis and guides therapy. Measures of kidney function usually are already available, but could remain within normal ranges for several decades.[2] To more accurately assess risk of progression to ESKD, either the PROPKD score or Mayo classification system often is used. The PROPKD score is based on sex, hypertension onset before age 35, urologic complications before age 35, and genotype.[16] Because genetic testing is not routinely done outside of a clinical trial, use of PROPKD is limited.

TABLE. **Basic optimized treatment of adults with ADPKD[20]**

Intervention	Goal	Methods to achieve goal
Intensive BP control	≤110/75 mm Hg in: 18- to 50-year-olds eGFR >60 mL/min/1.73 m^2 Particularly: Mayo Clinic class 1 C-E Intracranial aneurysm Valvular heart disease ≤130/85 mm Hg in: Other adult with hypertension	Early detection is essential[a] By order of preference: 1. ACEI/ARB 2. α/β or cardioselective β-blocker 3. Dihydropyridine CCB 4. Diuretic Dietary Approaches to Stop Hypertension (DASH)-like diet at early stages
Sodium	Moderate restriction (2.3 to 3 g/d) Adjust for extrarenal losses (hot climate, runners, sauna, bowel disease) if appropriate	Counseling Dietitian follow-up Monitor 24-hour urine sodium
Hydration	Moderately enhanced hydration spread out over 24 h (during the day, at bedtime, and at night if waking up) Maintain urine osmolality ≤280 mOsm/kg	Counseling Monitor first morning urine osmolality, plasma copeptin if available Water prescription (L) = [24-h urine solute load (mOsm) ÷ 280] + insensible loss (∫ 0.5L)
Protein	0.8 to 1 g/kg of ideal body weight	Dietitian Monitor protein intake: 6.25 x (UUN in g/d + [0.03 x weight in kg])
Phosphorus	Moderate diet phosphate restriction (800 mg/d)	Dietitian Read food labels and watch for food additives containing phosphates Use of phosphate binders not different from other advanced CKD when needed
Acid base	Maintain plasma bicarbonate within the normal range (≥22 mEq/L)	Increase fruits/vegetables (2 to 4 cups/day) Oral sodium bicarbonate if needed
Caloric intake	Maintain normal BMI Moderation in caloric intake	Dietitian Regular exercise
Lipid control	Aim for serum LDL-C ≤100 mg/dL	Dietitian Regular exercise Statin if needed (ezetimibe if intolerant to statin)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomular filtration rate; LDL-C, low density lipoprotein cholesterol; UUN, urine urea nitrogen.

[a]Screen children at risk every 3 years starting at age 5. Children with hypertension should be referred and managed by experts in pediatric hypertension

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The Mayo classification system categorizes patients with typical ADPKD into 5 prognostic classes.[17] Required data are the patient's age, height, and total kidney volume, as well as a single representative coronal image of the kidneys. The total kidney volume can be determined using an online calculator (available at: https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754). A benefit of the Mayo classification system is that it allows estimation of a patient's glomerular filtration rate (GFR) at any point in the future. However, it is not applicable to the approximately 5% of patients with ADPKD with an atypical presentation, ie, unilateral, asymmetrical, or segmental cyst burden.

TREATMENT

Goals

The focus of treatment is to slow disease progression and reduce the need for renal replacement therapy. Not to be forgotten, however, is the need to address the diminished quality of life experienced by patients with chronic kidney disease, particularly as the disease progresses.[18] In patients

with ADPKD, the physical burden caused by pain, abdominal fullness, cardiovascular disease, and urinary issues adds to the psychological burden stemming from treatment complexity and the hereditary nature of the disorder with its potential effect on family. Poor quality of life in patients with chronic kidney diseases has been shown to be associated with increased hospitalization and mortality rates.[19] Addressing quality-of-life issues beginning at the time of diagnosis and continuing over the patient's lifetime is a critical part of patient management and often requires involvement from other healthcare providers.

GENERAL MEASURES

The systemic consequences of ADPKD require a comprehensive treatment approach that includes a healthy lifestyle to enhance hydration, limit dietary sodium and protein intake, maintain a healthy weight, and reduce cardiovascular risk (**TABLE**).[20]

HYPERTENSION

Early in the course of ADPKD, before loss of kidney function, the activity of the renin-angiotensin-aldosterone system (RAAS) often increases and extracellular volume expands. These changes are thought to contribute to increased blood pressure observed in 50% to 70% of patients with ADPKD, with an average onset at age 30.[21-23]

An angiotensin converting enzyme inhibitor (ACEI) is generally recommended as first-line antihypertensive therapy based on the results of the HALT-PKD trials.[24,25] These trials were designed to determine the effect of intensive blockade of the RAAS and blood pressure control on the progression of kidney disease in individuals with an early or moderately advanced stage of ADPKD. In early ADPKD (eGFR >60 mL/min/1.73 m^2), the annual percentage increase in total kidney volume was not significantly different with the combination of the ACEI lisinopril and the angiotensin receptor blocker (ARB) telmisartan vs lisinopril plus placebo.[24] Similarly, there was no significant difference in change in eGFR between the 2 medication groups.[24] Lisinopril monotherapy resulted in greater decline in the left ventricular mass index and greater reduction in urinary albumin excretion. Similarly, in patients with ADPKD and stage 3 chronic kidney disease (eGFR 25 to 60 mL/min/1.73 m^2) monotherapy with lisinopril was sufficient to achieve blood pressure control (110/70 to 130/80 mm Hg); adding telmisartan offering no extra significant benefits.[25]

A key finding of the HALT-PKD trial is that rigorous blood pressure control (95/60 to 110/75 mm Hg), compared with standard blood pressure control (120/70 to 130/80 mm Hg), slowed the increase in total kidney volume with no overall change in the eGFR.[24] Secondary analysis confirmed that the kidney benefits were related to the degree of blood pressure control rather than pharmacologic intensity of RAAS blockade.[26]

PAIN

Pain associated with ADPKD could be acute or chronic.[2] Acute pain often is caused by kidney cyst hemorrhage, infection, or stones, while chronic pain generally is because of stretching or pulling of the kidney capsule caused by the enlarged kidneys or marked enlargement of the kidneys or liver that causes musculoskeletal back pain.[4] The pain etiology must be identified because some causes such as cyst infection could lead to severe systemic illness. Nonopioid analgesics, including short-term use of non-steroidal anti-inflammatory drugs, often are sufficient to provide relief for acute pain. Usual recommendations regarding analgesic use must be followed, such as dosing based on renal or liver function, age ≥65. Reserve opioids, often in combination with another analgesic, may be used for acute moderate-to-severe pain.

PREGNANCY

Women with ADPKD of reproductive potential should be advised that exogenous estrogen or progesterone exposure could aggravate ADPKD.[2] Family planning, which includes genetic counseling and preimplantation genetic diagnosis/*in vitro* fertilization access, could be offered.

CHILDREN

Current recommendations indicate that off-label use of vasopressin antagonists should be limited to children at high risk of early disease progression.[9] The use of somatostatin analogues and mTOR inhibitors (eg, sirolimus and everolimus) is not recommended, while the safety and efficacy of statin therapy are unclear. A low dietary salt intake is recommended.

TREATMENT OF RAPIDLY PROGRESSIVE DISEASE

Tolvaptan

Plasma levels of vasopressin and its precursor copeptin generally are increased in patients with ADPKD.[27,28] The plasma level of copeptin correlates with ADPKD severity and the rate of disease progression.[29] Therefore, the vasopressin system was identified as a therapeutic target, leading to development and FDA-approval of tolvaptan, a vasopressin V2-receptor antagonist.

FDA-approval of tolvaptan was based on the results of the TEMPO 3:4 phase III clinical trial involving 1445 adults age 18 to 50 with ADPKD, total kidney volume ≥60 mL, and creatinine clearance ≥60 mL/min.[30] After 3 years of treatment, tolvaptan significantly reduced the increase in total kidney volume and decline in kidney function compared with pla-

cebo. The rate of discontinuation was higher with tolvaptan vs placebo (23% vs 14%, respectively), primarily because of events related to aquaresis, ie, excretion of electrolyte-free water, such as thirst, polyuria, nocturia, polydipsia, as well as increases in liver enzyme levels >3 times the upper limit of normal.

The safety and efficacy of tolvaptan also have been demonstrated in patients with later-stage ADPKD (eGFR 25 to 65 mL/min/1.73 m^2 if age 18 to 55 or eGFR 25 to 44 mL/min/1.73 m^2 if age 56 to 65).[31] The adjusted mean change in eGFR over 1 year was significantly lower in the tolvaptan vs placebo group (-2.3 vs -3.61 mL/min/1.73 m^2, respectively; $P < .001$). The benefits of tolvaptan were maintained across subgroups, including sex, baseline eGFR, and stage of chronic kidney disease (except stage 2). Aquaretic and other adverse events led to 8.4% of patients withdrawing during a single-blind tolvaptan period before randomization. After randomization, the overall rates of new or worsening adverse events did not differ between the tolvaptan and placebo groups. After randomization, patients treated with tolvaptan had higher rates of polyuria, nocturia, thirst, polydipsia, dry mouth, diarrhea, and fatigue.

Tolvaptan is approved to slow decline in kidney function in adults at risk of rapidly progressing ADPKD. Patients at risk of rapid disease progression are those with Mayo class 1C, 1D, or 1E disease or PROPKD score ≥6. Most experience is in adults age ≤55 and eGFR ≥25 mL/min/1.73 m^2. The decision to prescribe tolvaptan should be made using a shared decision-making discussion with the patient based on risks (eg, liver toxicity, polyuria, polydipsia), benefits, and affordability. Assess for potential drug interactions. The morning and afternoon dosages are titrated over several weeks based on tolerability as well as alanine transferase and aspartate transaminase levels remaining <2 to 3 times the upper limit of normal.

Investigational therapies

Several medications are being investigated for treating ADPKD. These include tesevatinib, metformin, pioglitazone, nicotinamide, lixivaptan, and somatostatin analogs such as lanreotide. None is FDA-approved for ADPKD.

COLLABORATING WITH A NEPHROLOGIST

Managing patients with ADPKD should involve a nephrologist, ideally one in an ADPKD center of excellence.[2] Because of the complex treatment of these patients, close communication between nephrologist and family physician is critical. It is important to reach agreement as to who will assume responsibility for treating the extra-renal complications of ADPKD, such as hypertension. Integrating the management of these disorders into the holistic management of the ADPKD is a key role of the family physician.

PATIENT EDUCATION RESOURCES

- American Association of Kidney Patients [https://aakp.org/]
- American Kidney Fund [https://www.kidneyfund.org/kidney-disease/other-kidney-conditions/polycystic-kidney-disease.html]
- Genetic and Rare Diseases Information Center [https://rarediseases.info.nih.gov/diseases/10413/autosomal-dominant-polycystic-kidney-disease]
- National Human Genome Research Institute [https://www.genome.gov/Genetic-Disorders/Autosomal-Polycystic-Kidney-Disease]
- National Institute of Diabetes and Digestive and Kidney Diseases [https://www.niddk.nih.gov/health-information/kidney-disease/polycystic-kidney-disease/autosomal-dominant-pkd]
- National Kidney Foundation [https://www.kidney.org/atoz/content/polycystic]
- National Organization for Rare Disorders [https://rarediseases.org/rare-diseases/autosomal-dominant-polycystic-kidney-disease/]
- Polycystic Kidney Disease Foundation
  - ADPKD [https://pkdcure.org/what-is-adpkd/]
  - Patient Handbook [https://pkdfoundation.salsalabs.org/infopacketandpatienthandbook/index.html] ●

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