CLINICAL PRACTICE

Autosomal Dominant Polycystic Kidney Disease

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Shortly after being elbowed in the flank during a pickup basketball game, a 35-year-old healthy man has severe, colicky abdominal pain followed by gross hematuria. He is hospitalized, and a renal ultrasound scan reveals bilateral polycystic kidneys and liver cysts, previously unknown to the patient. The blood pressure is 160/100 mm Hg. The serum creatinine concentration is 0.9 mg per deciliter (80 μmol per liter). The pain subsides in 2 days with analgesics, rest, and fluids; the gross hematuria resolves in 4 days, although microscopic hematuria persists. How should his case be further evaluated and managed?

THE CLINICAL PROBLEM

Autosomal dominant polycystic kidney disease is an inherited systemic disorder with major renal manifestations and, in some cases, abnormalities in the liver, the pancreas, the brain, the arterial blood vessels, or a combination of these sites.[1] The disease affects approximately 300,000 to 600,000 Americans of either sex, and without racial predilection. Each child of an affected parent has a 50% chance of inheriting the mutated gene, which is completely penetrant. Autosomal dominant polycystic kidney disease arises as a spontaneous mutation in approximately 5% of cases. However, in about one fourth of newly diagnosed cases, patients report no history of the disease, indicating that many familial cases go undetected.

Affected patients have numerous fluid-filled cysts in the kidneys; these cysts may collect blood after mild or severe trauma or may be the site of pyogenic infection. In rare cases, a malignant neoplasm develops, although the incidence of renal cancer among affected patients is not increased, as compared with the incidence in the general population. Autosomal dominant polycystic kidney disease begins in utero, but signs of the disease may not be detected for several decades.

Autosomal dominant polycystic kidney disease is caused by mutations in either of the two genes encoding plasma membrane–spanning polycystin 1 and polycystin 2 (*PKD1* and *PKD2*, respectively). The polycystins regulate tubular and vascular development in the kidneys and other organs (liver, brain, heart, and pancreas)[2] and interact to increase the flow of calcium through a cation channel formed in plasma membranes by polycystin 2. A mutation of either polycystin can disrupt the function of the other, resulting in similar clinical presentations. However, mutations of *PKD1* are more common than mutations of *PKD2* (accounting for 85% of cases), are likely to be associated with more renal cysts,[3,4] and lead to renal insufficiency on average 20 years earlier (median ages at the time of death or end-stage failure, 53 and 69 years, respectively).[5]

According to current thinking, although every cell in a heterozygous person with

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autosomal dominant polycystic kidney disease carries one copy of the mutated *PKD* gene along with a normal allele, renal cysts form in only a tiny fraction of the tubules, primarily the collecting ducts. Current thinking is that cyst formation occurs after an epithelial cell sustains a second genetic "hit" that compromises the function of the normal allele[6,7] (Fig. 1).

Liver cysts develop in more than 80% of patients with autosomal dominant polycystic kidney disease, and the cysts are usually larger in women than in men. Hypertension often occurs in childhood and affects nearly all patients in whom renal insufficiency develops.[8] Gross and microscopic hematuria are common (present in 60% of patients overall).[9] Young persons who participate in contact sports may have gross hematuria as the presenting sign of autosomal dominant polycystic kidney disease, but this complication may also occur without antecedent abdominal trauma.[10] Pyelonephritis and renal-cyst infections are serious problems requiring aggressive antimicrobial therapy.[11] Brain aneurysm occurs in approximately 8% of patients, which is about twice the prevalence in patients without mutations[12]; a family history of aneurysm increases the risk.[13,14] Kidney failure requiring renal-replacement therapy occurs in approximately 50% of patients and typically develops in the fourth to sixth decade of life.[1]

Figure 1 (facing page). Cyst Development in Renal Tubules.

In a cell that has one allele carrying the genetic mutation, a second "hit" to the normal allele propels perpetual proliferation, causing a bulge to form in the wall of the tubule. Further expansion is caused by cyclic AMP (cAMP), epidermal growth factor, and insulin-like growth factor. The cyst is in fact a benign renal tubular neoplasm that expands by increasing the mass of proliferating mural epithelial cells that surround a cavity filled with fluid. Cyst formation begins in utero and continues throughout life. The expanding cyst causes changes in the tubular basement membrane beneath it. Macrophages and fibroblasts, forerunners of fibrosis, appear in the interstitium. Most of the cysts that reach 2 mm in diameter have separated from the parent nephrons, becoming autonomous tumors as cellular proliferation and fluid secretion join to promote progressive enlargement; cAMP stimulates cyst growth by increasing the rate of cellular proliferation and by stimulating the rate of fluid secretion into the cysts.

STRATEGIES AND EVIDENCE

DIAGNOSIS

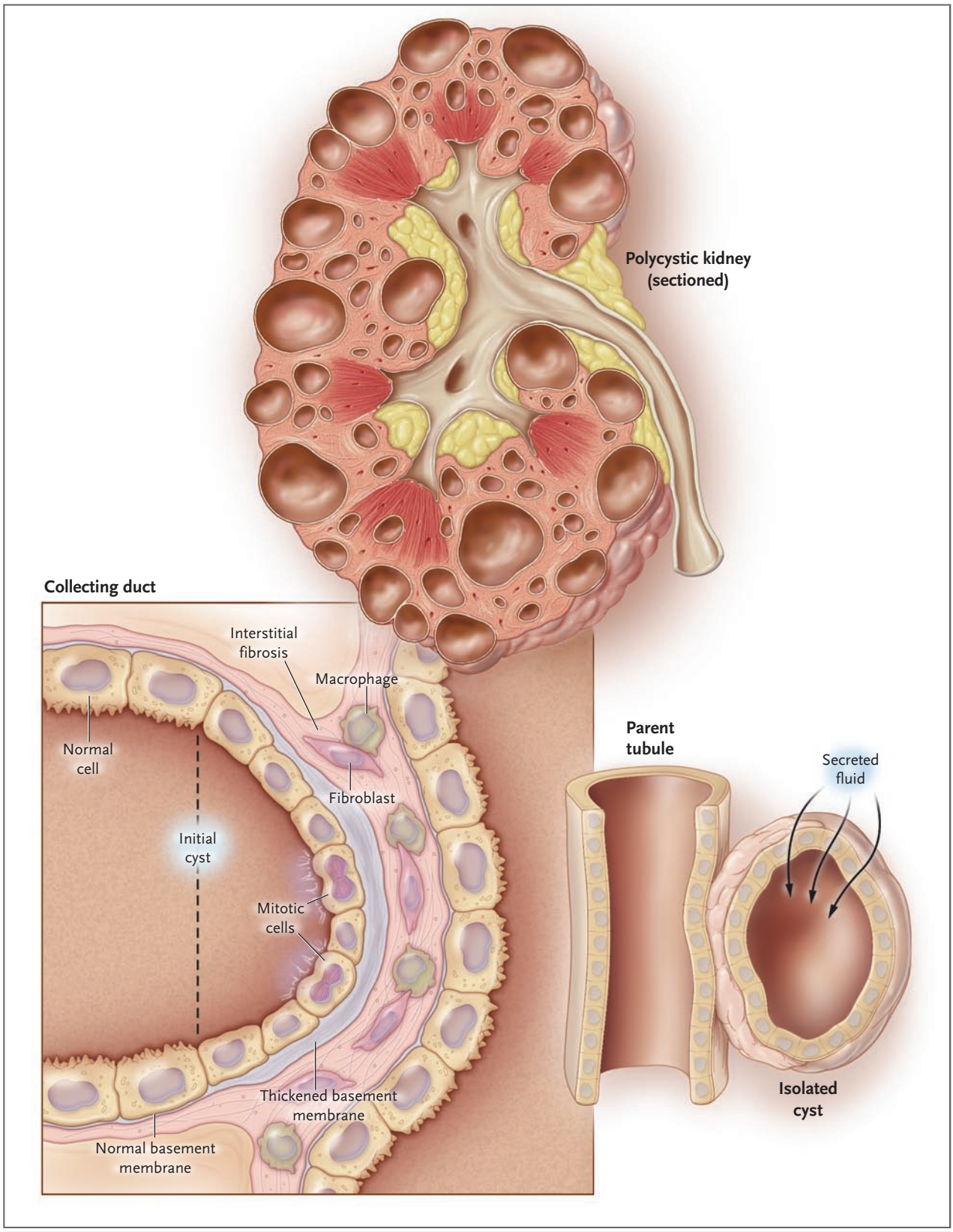
In adults with a positive family history, the diagnosis of autosomal dominant polycystic kidney disease is established by radiologic evidence of bilateral, fluid-filled renal cysts. Ultrasonography reliably detects cysts that are 1 cm or larger in diameter and is highly sensitive for the diagnosis in adults (Fig. 2B).[15] Criteria for the diagnosis include at least two unilateral or bilateral cysts in persons younger than 30 years of age, at least two cysts in each kidney in persons 30 to 59 years of age, and at least four cysts in each kidney in persons 60 years of age or older.[16] In patients with a few small or indistinct cysts, T_2-weighted magnetic resonance imaging (MRI) is more sensitive and identifies renal cysts as small as 3 mm in diameter (Fig. 2A).[4] Contrast-enhanced computed tomography (CT) is equally sensitive but involves the use of ionizing radiation and iodinated rather than gadolinium-containing contrast medium (Fig. 2C).[17] The identification of associated liver cysts, pancreatic cysts, or both confirms the diagnosis of autosomal dominant polycystic kidney disease. In patients who do not have a family history of the disease, it must be differentiated from other renal cystic disorders on the basis of radiologic and clinical features (Table 1).

MONITORING FOR DISEASE PROGRESSION

The development of arterial hypertension signifies disease progression and should be treated aggressively, with target levels of 130/80 mm Hg or below in adults and levels at or below the 75th percentile in children.[18]

Sequential measurements of serum creatinine concentrations are routinely performed in patients with autosomal dominant polycystic kidney disease but are insensitive measures of disease progression, especially in young patients. The glomerular filtration rate (GFR) typically remains within the normal range for several decades, despite progressive renal enlargement.[1] Compensatory hyperfiltration in surviving nephrons initially maintains serum creatinine levels at or near normal values; when levels start to rise appreciably above baseline, more than 50% of functioning parenchyma has been destroyed.[1]

Imaging studies (ultrasonography, MRI, or CT) are useful in estimating kidney volume, which appears to be predictive, at any given age, of the subsequent rate of progression and the risk of renal insufficiency.[3] The combined volume of poly-



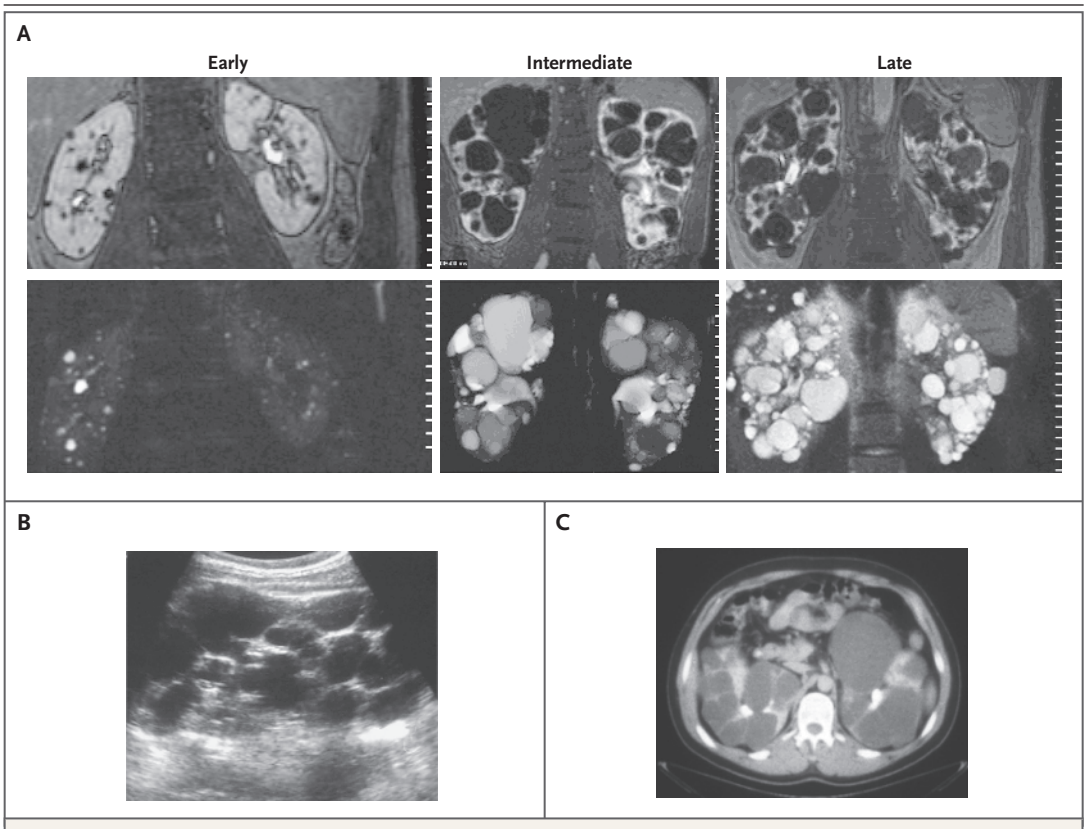


Figure 2. Radiologic Features of Autosomal Dominant Polycystic Kidney Disease.

Panel A shows paired T_1-weighted and T_2-weighted MRI scans from three patients with a normal glomerular filtration rate (GFR) but different stages of disease progression. The T_1-weighted images (top row) were obtained after intravenous infusion of gadolinium to highlight functioning parenchyma. Cysts appear as black holes interspersed on a blanket of bright parenchyma. The renal pelvis contains highly concentrated gadolinium. As the disease progresses, the cysts become more numerous; the largest cysts in each kidney are the oldest. In the late stage, there is sufficient functioning parenchyma to maintain a normal GFR despite massive distortion. On the T_2-weighted images (bottom row), the cysts are bright. Cysts as small as 3 mm in diameter can be detected. Panel B shows an ultrasound scan from a patient with an advanced case of autosomal dominant polycystic kidney disease. Cysts are identified by the dark areas. The axial CT scan in Panel C, from a patient with a slightly decreased GFR (stage 2 chronic kidney disease), shows functioning parenchyma enhanced by intravenously administered contrast material. Concentrated contrast material can be seen in patches between cysts and in the renal pelvis.

cystic kidneys in adults commonly exceeds 1000 ml, as compared with normal volumes of 308 ml in women and 404 ml in men.[1,3,19] The annual rate of increase in kidney volume ranges from less than 1% to more than 10% (Fig. 3). The two kidneys usually enlarge relatively symmetrically and at a steady rate[3]; unilateral enlargement is rare. Variation in the rate of enlargement may largely account for the wide range of ages at which kidney function fails. Combined kidney volumes exceeding 1500 ml are frequently associated with a decreased GFR.

GENETIC TESTING

Autosomal dominant polycystic kidney disease can be caused by hundreds of different intragenic *PKD1* and *PKD2* mutations. Since current genotype testing can identify only approximately 70% of the known pathogenic mutations, it is not a useful screening tool.[20]

SCREENING FOR BRAIN ANEURYSM

Magnetic resonance angiography is routinely recommended for patients who have a family history of aneurysm or stroke and for any patient with

Table 1. Other Renal Cystic Disorders.*

Condition	Number of Cysts	Renal Cyst Distribution	Age at Detection	Distinguishing Features
Simple cysts	Few	Diffuse	All ages	Benign
Acquired cystic disease	Few to many	Diffuse	Adulthood	Cyst development preceded by renal failure
Tuberous sclerosis	Few to many	Diffuse	All ages	Renal angiomyolipomas; may be associated with dermatologic findings (adenoma sebaceum, café au lait patches), periungual fibroma, retinal hamartomas, or cardiac rhabdomyoma
Autosomal recessive polycystic kidney disease	Many	Radial pattern	Often present at birth; childhood in some cases	Huge kidneys; associated with congenital hepatic fibrosis
Hereditary cystic diseases with interstitial nephritis	Few to many	Medullary	Childhood; adulthood in a few cases	Early renal failure; may be associated with retinitis pigmentosa, truncal cerebellar ataxia, or gout

* Conditions are listed in order of decreasing prevalence. Information is from Torres and Grantham.[1]

known autosomal dominant polycystic kidney disease who has new-onset or severe headache or other troubling central nervous system symptoms or signs.[21] In the absence of a family history of aneurysm, screening is not routinely recommended for asymptomatic patients.

TREATMENT

There are currently no treatments that have been shown in randomized trials to slow the formation of cysts or disease progression. Recommended therapies are tailored to the age of the patient and to troubling signs and symptoms.

Hypertension and Left Ventricular Hypertrophy

Hypertension is present in 35% of children with autosomal dominant polycystic kidney disease and is associated with abnormal thickening of the left ventricular wall.[8,9,22] Treatment, which is recommended for adults with blood pressure exceeding 130/80 mm Hg and for children with blood pressure exceeding the norm for sex and age (www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm), includes salt restriction and antihypertensive therapy. Angiotensin-converting–enzyme (ACE) inhibitors or angiotensin II–receptor blockers (ARBs) are preferred, since a retrospective analysis has shown that treatment with these agents, as compared with other antihypertensive therapies, is associated with preservation of renal function in patients with autosomal dominant polycystic kidney disease.[23] Plasma volume expansion frequently accompanies the disease and may reduce the effects of ACE-inhibitor and ARB therapy. If salt restriction and ACE-inhibitor and ARB therapy fail to lower blood pressure sufficiently, it may be necessary to provide treatment with diuretics (thiazides initially, with a switch to loop diuretics if thiazides are not effective).

Hematuria

When gross hematuria first occurs, it can be frightening for the patient. CT or MRI studies may identify intraparenchymal or extrarenal hemorrhage, bleeding into the urinary collecting system, or solid tumors, which are rare. Renal colic due to clots in the collecting system can be severe. Bed rest, analgesics, and hydration sufficient to increase the urinary flow rate to 2 to 3 liters per day are recommended; hematuria generally declines to microscopic levels in a few days. Patients should be instructed in self-treatment for straightforward repeat episodes. The use of anticoagulants, including low-dose aspirin, should be avoided in the absence of a strong indication in patients with a history of gross hematuria. All patients should be counseled to avoid sports in which abdominal trauma may occur (e.g., boxing and rugby).

Urinary Tract Infection

Women are more susceptible to urinary tract infections than are men and have a higher incidence

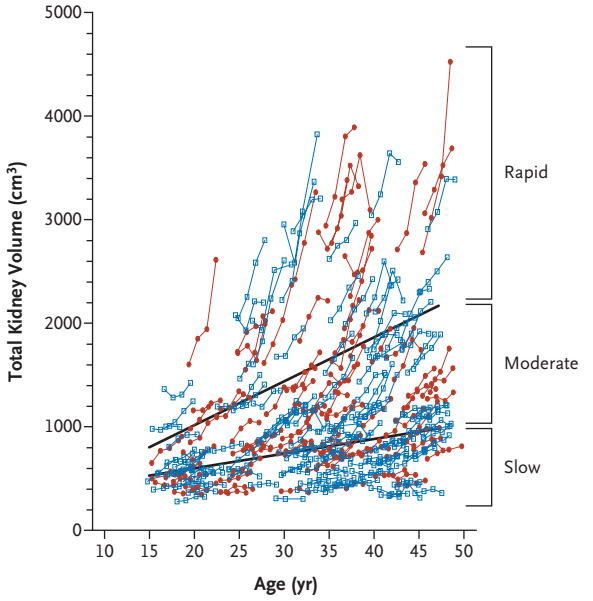


Figure 3. Relation between Age and Total Kidney Volume in Patients with Autosomal Dominant Polycystic Kidney Disease.

Total kidney volume (the sum of the volumes of the left and right kidneys) is shown in 232 women (blue data points) and men (red data points) studied over a 3-year period.[3] The total kidney volume increased progressively in most patients but at widely differing rates. The two black lines superimposed on the data points demarcate slow, moderate, and rapid rates of progression. The rate of disease progression in individual adults at any age can be determined by measuring kidney length, width, and thickness on MRI, CT, or ultrasound scans and estimating the kidney volume with the ellipsoid equation.[15]

of parenchymal and cyst infections. Coliforms are the most common pathogens. Treatment of common lower urinary tract infections in women with autosomal dominant polycystic kidney disease is the same as that in the general population of women with such infections.[11] In men, radiologic and urologic evaluation is indicated. Acute pyelonephritis and symptomatic cyst infection require hospitalization, with blood and urine cultures. Fluoroquinolones, administered intravenously until fever, renal pain, and leukocytosis abate, are considered the agents of choice for these infections in both women and men.[24]

Renal Stones

Nephrolithiasis is approximately twice as prevalent in patients with autosomal dominant polycystic kidney disease as in the general population, and uric acid stones are more common than calcium oxalate stones.[25] CT scanning is sensitive for identifying stones, and management generally involves the same strategies as in patients without autosomal dominant polycystic kidney disease.[26]

Renal Pain

Flank or abdominal pain usually accompanies renal infection, cyst hemorrhage, or renal stones; however, severe pain may also occur in the absence of other apparent renal complications.[27] Patients with chronic, unrelenting pain may require the care of a specialist in pain management; uncontrolled studies have suggested potential benefits of analgesics, transcutaneous stimulation, local injections of anesthetics, and laparoscopic or open surgical unroofing of cysts.[28] Laparoscopic renal denervation was recently shown to markedly decrease pain for more than 2 years in 12 children whose pain was inadequately controlled by narcotics.[29] This treatment warrants further evaluation, including in adults.

Renal Insufficiency

The usual age at which end-stage renal disease develops in patients with autosomal dominant polycystic kidney disease increased by 10 years between the period from 1985 to 1992 and the period from 1992 to 2001; it has been suggested that this improvement may be attributable to the increased use of renin–angiotensin system inhibitors for the management of hypertension.[23,30,31] A controlled trial, the Halt Progression of Polycystic Kidney Disease study (ClinicalTrials.gov number, NCT00283686), is under way to determine whether treatment with ACE inhibitors and ARBs, administered singly or in combination, will reduce the rate of increase in kidney volume and slow the decline in GFR.

When dialysis is required, either peritoneal dialysis or hemodialysis may be used. However, abdominal hernias, which are common in patients with autosomal dominant polycystic kidney disease, may complicate peritoneal dialysis, whereas the use of heparin anticoagulation for hemodialysis can be problematic in patients with hematuria.

The outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease are generally similar to the outcomes in patients without the disease.[32] Identification of related living donors should include the use of renal T_2-weighted MRI to rule out the disease (Fig. 2A). If the MRI findings are not definitive, genetic

testing can be performed in the donor to look specifically for the recipient's mutation, assuming that it has been identified.

WOMEN

Women with autosomal dominant polycystic kidney disease may have massive cystic enlargement of the liver,[1] a complication attributed to the role of estrogens in promoting the growth of cysts. Exogenous estrogens and repeated pregnancies are risk factors for this complication. Massive liver enlargement is usually not seen until midlife. It is prudent to avoid the use of estrogenic products in women with liver cysts; if prescribed, they should be given in the lowest effective doses, and transdermal administration (which delivers less hormone to the liver than other routes of administration) may be preferable, although it has not been formally studied in patients with polycystic kidney disease. If liver enlargement reduces the quality of life, partial hepatectomy can be performed; good outcomes have been reported at experienced centers.[33]

Pregnancies in women with autosomal dominant polycystic kidney disease who do not have hypertension or renal insufficiency are generally uncomplicated. However, the risks of severe hypertension and preeclampsia (and associated complications) are higher than those in the general population when elevated blood pressure or renal insufficiency is present before conception.[34]

AREAS OF UNCERTAINITY

SCREENING

Screening of asymptomatic children by means of radiologic studies or genetic testing is not currently advocated, since no intervention has been shown to be effective in preventing cyst formation. Because autosomal dominant polycystic kidney disease is inherited, screening should be offered to persons who are 18 years of age or older if they expect to have children. The patient should understand that the knowledge that he or she has the disease may cause stress and may hinder the purchase of life insurance. However, in the United States, discrimination in health insurance, but not life insurance, and employment on the basis of genetic information is prohibited by the Genetic Information Nondiscrimination Act of 2008. Diagnosis early in adulthood allows for the possibility of reproductive planning, including the potential use of preimplantation genetic diagnosis and embryo selection to avoid genetic transmission.[35]

PREVENTION OF DISEASE PROGRESSION

Studies in laboratory animals with cystic kidneys indicate that renal inflammation has the potential to accelerate disease progression.[36-38] In addition, polycystic kidneys in humans may harbor occult microorganisms.[39,40] Further study is needed to determine whether occult infection plays a role in the initiation and growth of cysts.

Cyclic AMP (cAMP) increases the proliferation of epithelial cells in cyst walls and increases the rate of fluid secretion into cysts. Thus, stimuli for increased cAMP production should be avoided. These include some herbs, such as forskolin, which is extracted from the roots of *Coleus forskolii* and marketed as a potential treatment for numerous conditions,[41] and proprietary "health foods" that have not been evaluated carefully. Long-term use of agents that increase the production of cAMP within cyst cells (caffeine, theophylline, β-adrenergic agonists, and secretin) is also a theoretical concern.[42,43]

Arginine vasopressin (AVP) is a potent activator of renal adenyl cyclase. In rodents with various renal cystic disorders, pharmacologic inhibition of AVP-V2 receptors reduces renal growth and preserves renal function.[44] The usefulness of AVP-V2 inhibitors in slowing the progression of renal enlargement and insufficiency in patients with autosomal dominant polycystic kidney disease is currently being evaluated in a placebo-controlled trial (NCT00428948).

Maintenance of ideal body weight, regular exercise (preferably walking or swimming), and a diet limited in salt (approximately 6 g of sodium chloride daily) and protein (no more than 1 g per kilogram of body weight per day) are prudent recommendations, although they have not been explicitly studied in patients with polycystic kidney disease.

WATER INTAKE

In humans, the osmolality of urine far exceeds that of plasma (approximately 285 mOsm per kilogram) most of the time, reflecting the sustained action of plasma AVP.[45] Although data from randomized trials are lacking, patients with autosomal dominant polycystic kidney disease who have normal renal function (creatinine clearance, more than 90 ml per minute per 1.73 m^2 of body-surface area)

might potentially benefit from frequent water intake that would be sufficient to reduce plasma AVP levels and decrease the average urine osmolality, bringing it closer to that of plasma. For persons with an average output of urine (approximately 1500 ml per day) and solute (approximately 900 mOsm per day), approximately 3000 ml of water consumed throughout waking hours would reduce average plasma AVP levels by about one half. This amount of fluid is widely recommended for persons with kidney stones but must be prescribed cautiously. Hyponatremia is a concern in patients who are following low salt diets or taking diuretics,[46] as do many patients with autosomal dominant polycystic kidney disease, and monitoring of the sodium level is prudent in such patients.

GUIDELINES

There are no guidelines from professional societies for the treatment of patients with autosomal dominant polycystic kidney disease.

CONCLUSIONS AND RECOMMENDATIONS

Gross hematuria after trauma, as in the patient described in the vignette, is a classic presenting feature of autosomal dominant polycystic kidney disease. Approximately 75% of such patients have a family history of the disease, yet many have no overt manifestations until the third or fourth decade of life, when hypertension or abdominal pain may be the first sign. In patients with a positive family history, identification of numerous cysts in the kidneys confirms the diagnosis of autosomal dominant polycystic kidney disease; in the patient described in the vignette, the renal findings and liver cysts establish the diagnosis. With only supportive therapy, gross hematuria usually subsides within days. Patients should be encouraged to avoid situations that carry a high risk of abdominal trauma (e.g., high-impact sports). Blood pressure should be maintained below 130/80 mm Hg. If pharmacologic therapy is needed, I would recommend an ACE inhibitor or ARB, on the basis of limited observational data suggesting a benefit of these agents in polycystic kidney disease, while awaiting data from a randomized trial assessing their effects on the progression of disease. In addition, I would recommend a diet low in salt (no more than 6 g of sodium chloride daily) and protein (1 g per kilogram) and would also suggest sufficient intake of water (and noncaffeinated beverages) for excretion of 2 to 3 liters of urine per day (as a means of lowering AVP levels, which may stimulate cyst growth), although these approaches have no proven benefit in patients with polycystic kidney disease. Estimation of total kidney volume (by means of ultrasonography or MRI) suggests the extent to which the disease has progressed. The patient should be advised to inform his first-degree adult relatives of the diagnosis, and screening should be offered to them. I would encourage the patient to participate in one of the clinical trials of targeted therapy for autosomal dominant polycystic kidney disease. Useful Web sites for patient education include www.pkdcure.org, www.kidney.org, and www.nlm.nih.gov/medlineplus.

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