AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: REVIEW AND MANAGEMENT UPDATE

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited nephropathy. Initially, it is characterised by the growth of renal cysts. Later, progressive deterioration of renal function determines the prognosis of ADPKD, depending on the main factors of progression (genetic, renal volume, and hypertension). Ultrasonography is the diagnostic technique of choice in the screening for relatives of ADPKD patients. Due to the absence of specific treatment it is necessary, in many cases, to start with renal replacement therapy. ADPKD can also be associated with extrarenal manifestations, mainly polycystic liver disease and cerebral aneurysms, which contribute to increased morbidity and mortality of these patients.

Keywords: Autosomal dominant polycystic kidney disease (ADPKD), diagnosis, cysts complications, renal disease progression, extrarenal manifestations.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited renal disease with an estimated prevalence of approximately 1 in 800 live births. It is caused by mutations in two genes: *PKD1* in 85% and *PKD2* in 15% of cases.[1] Offspring have a 50% risk of inheriting the mutated gene; however, there are sporadic mutations in 10-15% of patients. ADPKD is the cause of 6-10% of patients undergoing renal replacement therapy (RRT).[2]

The *PKD1* and *PKD2* genes encode for proteins polycystin 1 and polycystin 2, respectively, which are an associated complex in the cell membrane, acting as a receptor and non-selective cation channel.[3] The polycystin complex is localised mainly in the primary cilium of the tubular epithelium, but also in focal adhesions between cells and cell-matrix. Its functions are receptor-sensor of the urinary flow, orientation of the cell, and regulation of the cell cycle.

In ADPKD, these alterations in cilia function cause a cascade of biochemical signals with the increase of intracellular cyclic adenosine monophosphate (cAMP)[4] that stimulate cell proliferation and transverse growth instead of longitudinal tubule. The cell loses its orientation,[5] initiating the formation of renal cysts. The Na-K-ATPase pumps translocate from the basolateral membrane to the luminal membrane, whereby promoting sodium and water secretion into the cyst, stimulating its growth.[6]

With reference to the *two-hit* hypothesis, the second hit could explain the variable phenotypic expression of the disease in families with the same mutation and all renal cysts are forming only from 1% of tubular cells. Although a mutated allele is inherited, cyst genesis begins when a somatic mutation in the normal allele (*second hit*) appears.[7] The severity of ADPKD in the individual depends on the precocity of this mutation occurring, as has been observed in experiments with mice.[8] Environmental factors (chronic inflammation, cytokines, renal ischaemia) may accelerate this process.[9]

The progressive growth of renal cysts can cause tubular obstruction and renal ischaemia, which increase activity of the renin-angiotensin system (RAS) with arterial hypertension.[10] Deterioration of renal function is not observed until the destruction of at least 50% of the parenchyma. Histological lesions are hyperplasia of the cystic epithelium,

vascular sclerosis, and interstitial fibrosis. The kidneys increase their volume greatly.

DIAGNOSIS

Screening diagnosis should be performed in all first-degree adult relatives (>18 years) of patients with ADPKD.[11] Ultrasonography is the technique of choice to diagnose and follow-up ADPKD patients, detecting cysts >1 cm and abdominal extrarenal features such as hepatic cysts. Ultrasonography is cheap and safe, and its sensitivity for *PKD1* is significantly higher than for *PKD2*.[12] Computed tomography (CT) and magnetic resonance imaging (MRI) can detect cysts as small as 0.5 cm but are reserved for limited cases (suspicion of kidney stones or renal tumours) as they are more expensive and expose patients to radiation. MRI is the best imaging modality to monitor renal volume as used in research studies but not in clinical practice.[13]

Ultrasonographic diagnostic criteria[14] are applied to patients with unknown genotype and a family history of ADPKD (Table 1). In the case of a negative family history, the presence of renal cysts with increased kidney size, deterioration of renal function, and liver cysts may suggest the diagnosis of ADPKD;[15] however, it must be differentiated from other cystic acquired disorders (multiple simple cysts, acquired renal cystic disease, medullary sponge kidney) or genetic disorders (autosomal recessive PKD, tuberous sclerosis, orofaciodigital syndrome Type 1, medullary cystic disease).[16]

Genetic testing should not be used as a screening tool when imaging diagnosis is clear. It is only indicated in specific situations: diagnosis of exclusion in younger at-risk individuals with a family history of ADPKD (such as a potential living-related kidney donor), patients with cystic disease but without affected relatives, individuals with early onset of PKD in families with ADPKD, and couples who wish a prenatal or preimplantation genetic diagnosis.[17] There are two methods to perform genetic testing: genetic linkage analysis (indirect study that requires several affected family members) or mutation analysis by Sanger sequencing (direct study, useful in sporadic mutations).[18]

Urinary Findings

The urinary concentration defect is one of the earliest findings and may be associated with symptoms of thirst and polyuria.[19] It has been demonstrated that urinary osmolality is less in

Table 1: Ultrasonographic criteria diagnosis for patients with a positive family history of autosomal dominant polycystic kidney disease.

Years	Number Of Cysts
15-39	≥3 cysts (unilateral or bilateral)
40-59	≥2 cysts in each kidney
>60	≥4 cysts in each kidney
>40	<2 cysts for diagnosis of exclusion

ADPKD after water restriction test.[20] Proteinuria is usually minimal and is associated with more advanced renal dysfunciton.[21] Urolithiasis occurs in 20-36% of cases, mainly because of the cystic collector compression system.[22] In addition, the stones are favoured by other alterations in the urine which may be present: low urine pH, hypocitraturia, hyperoxaluria, or hypercalciuria.

Cyst Compilations

Cystic infection causes sudden acute pain, localised in the flank, and fever with elevated markers of inflammation. Imaging tests should be performed for diagnosis since blood or urine cultures are often negative.[23] The treatment of choice is soluble antibiotics (quinolones) that penetrate the walls of the cyst for several weeks. Depending on the severity of infection, other treatment options to consider are percutaneous or surgical drainage, or even nephrectomy in recurrent infections.

In symptomatic cystic bleeding, the management is typically conservative with rest, hydration, and analgesia. In persistent bleeding, the following may be necessary: transfusion, desmopressin, percutaneous embolisation, or nephrectomy.[24] When haematuria persists for more than 1 week or when the first episode occurs in over 50 years, screening for kidney cancer with MRI or CT with contrast is recommended. The prevalence of kidney cancer is not increased in patients with ADPKD.[25]

RENAL DISEASE PROGRESSION

Although during the first decades of life the renal function remains normal, the growth and development of renal cysts continues. After starting the deterioration, the annual reduction of glomerular filtration rate (GFR) is 4.4-5.9 ml/minute.[26] Depending on the GFR, the patients

should be regularly monitored by the nephrologist, although there are no established protocols. ADPKD is considered by some authors the prototype of cardiorenal syndrome Type 4,[27] associated with lower prevalence of cardiovascular disease. The main factors that determine progression of chronic kidney disease (CKD) are: genetic, renal volume, and hypertension (Table 2).

The mutation in *PKD1* has a worse prognosis, beginning the RRT several years before *PKD2* (53 years versus 69 years). A recent study in patients with *PKD1* observed that individuals with *truncating mutations* progress faster to RRT than patients without this mutation (55 years versus 67 years).[28]

Total renal volume is the best predictor of progression of CKD.[29] The increase of renal volume rate is 1-10% per year. Data from CRISP (Consortium for Radiologic Imaging Studies of polycystic kidney disease) of kidney volume, measured by MRI, demonstrated that the growth in renal volume is associated with deterioration of renal function,[30] reduction of blood flow renal,[31] and hypertension.[32]

The control of blood pressure slows the progression of CKD and usually precedes the decline of GFR.[33] Initial treatment option is the use of RAS inhibitors to achieve blood pressure of <130/80 mmHg;[34] however, these have not demonstrated superiority in the progression of CKD versus beta-blockers[35] or calcium channel blockers,[36] only with diuretics.[37] 45% of ADPKD patients have a non-dipping circadian rhythm on ambulatory blood pressure monitoring.[38]

Table 2: Factors that determine progression of CKD in ADPKD patients.

Major	Minor
Genotype	Early onset of symptoms
PKD1 > PKD2	Proteinuria
TRV	HDL cholesterol
TRC	Defect in urinary concentration
Hypertension	LVH

CKD: chronic kidney disease; ADPKD: autosomal dominant polycystic kidney disease; TRV: total renal volume; TRC: total renal cyst; HDL: high-density lipoprotein; LVH: left ventricular hypertrophy.

Others relevant factors include: early age of onset of symptoms,[39] low high-density lipoprotein cholesterol levels, proteinuria, haematuria, left ventricular hypertrophy, and defect in urinary concentration (Table 2).[40] Although traditionally the male sex has been considered a risk factor for progression, in many articles there are no differences.[41] Normotensive pregnant women with normal renal function usually have uncomplicated pregnancies without reduction of GFR; however, several pregnancies may accelerate progression to CKD.[42]

TREATMENT

Experimental studies with vasopressin V2 receptor antagonist (tolvaptan) in mice with PKD found lower renal cAMP levels and inhibition of cystogenesis.[43] The TEMPO study included 1,445 ADPKD patients with GFR >60 ml/minute and renal volume >750 ml, who received treatment with tolvaptan or placebo (double-blind) for 3 years. In the results of the tolvaptan group, a slowing of the deterioration in renal function was observed and there was a smaller increase in renal volume, although adverse effects were higher (hypernatraemia, polyuria, or hyperuricaemia).[44] Other treatments, such as somatostatin analogues[45] and the mammalian target of rapamycin (mTOR) inhibitor[46] have shown no beneficial effect in these patients.

RRT is required in 50% of patients older than 60 years. In recent years, it has been observed that the age at initiation of RRT has increased, attributable to therapeutic advances. However, one study found no difference in the last 25 years in ADPKD patients who started RRT, despite a delay of 9 years in the age of onset of RRT in patients without ADPKD.[47]

Kidney transplantation is the best therapeutic choice for ADPKD patients in RRT.[48] Nephrectomy is indicated previously in presence of repeated cystic infections or bleeding and when an enormous renal size may complicate a correct placement of the graft. Peritoneal dialysis is a technique of first choice[49] which gives a better prognosis than haemodialysis for some authors;[50] however, in patients with massive polycystic liver disease, very large kidneys, abdominal hernias, or recurrent diverticulitis it is not recommended.

In most articles, the survival of the ADPKD patients in RRT was higher than non-ADPKD patients, may be in relation to: starting RRT at younger age, lower prevalence of cardiovascular risk factors,

and higher haemoglobin levels.[51] In another study, ADPKD patients showed a higher survival rate than diabetes-free non-ADPKD patiens.[52] The primary cause of death in these patients was cardiovascular disease, followed by infections.[53,54]

EXTRARENAL MANIFESTATIONS

Polycystic liver disease is the most common extrarenal manifestation and is associated with increased renal volume, older age, and female sex[55] (several pregnancies or oestrogen intake),[56] as oestrogen can stimulate cyst hepatic growth. Liver cysts are usually asymptomatic and the liver function is normal, so follow-up of these patients is not necessary. The diagnosis is performed by ultrasonography; however, MRI is more sensitive for the detection of small cysts.[57]

The increased liver volume may cause symptoms of extrinsic compression: abdominal pain, early satiety, and obstruction of the hepatic veins or biliary duct.[57] Partial hepatic resection or even liver transplantation may be necessary in the case of massive polycystic liver.[58] Treatment with somatostatin analogues for 2 years has shown decreased liver volume but more studies are needed. The mTOR inhibitors have not obtained any results.[59] Liver cyst infection causes fever, right upper abdominal pain, and possible elevated CA19.9 and alkaline phosphatase levels. Treatment consists of antibiotics that penetrate the cyst wall, and the response to percutaneous drainage is better than in cysts kidney.[60]

The prevalence of cerebral aneurysms (CA) is 5-times higher in the general population and is increased with a positive family history of CA.[61] A rupture of a CA, resulting in an intracerebral or subarachnoid haemorrhage, is the most severe complication of ADPKD,[62] and depends on size of the CA and other factors such as age, uncontrolled hypertension, tobacco, cocaine, or anticoagulants.[63] Patients with CA are usually asymptomatic.

Magnetic resonance angiography (MRA) or CT angiography are the procedures of choice for diagnosis of CA.[64] Screening is indicated in ADPKD patients with previous family history of aneurysm or cerebral bleeding, previous rupture, or neurological symptoms.[65] In high-risk patients, when the diagnostic test detects no aneurysms, it should be repeated every 5 years. When an aneurysm is diagnosed, the therapeutic options are:[66] conservative management with

radiological monitoring in CA <7 mm, and surgical intervention or endovascular repair[67] in AC >7-11 mm or rapidly growing.

With regards to cysts in other organs, heart or abdominal manifestations are less common and usually asymptomatic so screening is not recommended. The cysts in the epididymis and seminal vesicles are a rare cause of infertility,[68] arachnoid cysts are usually asymptomatic, although they may increase the risk of subdural haematoma, and there does not appear to be an increased risk of ovarian cysts.[69]

Left ventricular hypertrophy is the most frequent cardiac manifestation, usually associated with hypertension, but it has also been observed in normotensive patients.[70] The mitral valve prolapse is the most common valve disease;[71] others that are less common are tricuspid valve prolapse and aortic regurgitation due to aortic root dilatation, which increases the risk of aortic dissection. Studies suggest an increased incidence of coronary and aortic abdominal aneurysms.[72] The increased risk of colonic diverticula and abdominal hernias in ADPKD patients may contraindicate the peritoneal dialysis.[73]

CONCLUSIONS AND RECOMMENDATIONS

ADPKD is a hereditary systemic disorder characterised by the growth of renal cysts. The first symptoms appear from adulthood, such as hypertension, haematuria, nephrolithiasis, or cyst complications (infection and bleeding) that usually are due to the number and size of renal cysts. Total renal volume is the best predictor of prognostics for ADPKD, and factors of progression of CKD should be controlled.

ADPKD patients should be regularly followed-up by the nephrologist with renal function and ultrasonograhy, and screening diagnosis should be performed in all first-degree adult relatives with ultrasonograhy. A diet low in salt (<6 g/day) and protein (<1 g/day) is recommended. Blood pressure should be maintained at <130/80 mmHg since the treatment of choice is RAS inhibitors. In addition, ADPKD patients should drink 2-3 litres of water per day and avoiding caffeine, which may stimulate cAMP levels and cystogenesis. It is recommended to normalise cholesterol levels with diet or treatment. A ruptured cerebral aneurysm is the most severe complication, so screening

with MRA should be performed in high-risk ADPKD patients.

Despite the absence of a specific treatment for ADPKD as yet, the initial results of treatment with tolvaptan showed a slowing reduction in deterioration of renal function and a smaller increase in renal volume; however, comparisons with more long-term studies are necessary in the search for a definitive treatment. Therefore, we should follow the recommendations in this review to slow the progression of CKD in ADPKD patients.

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