Chapter 3

Treatment and Management of Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening single-gene disease. It affects up to 15 million people worldwide with 50% risk for end-stage kidney disease, 80% risk for hypertension, 60% risk for painful kidney complications, 20% risk for symptomatic polycystic liver disease and 3% risk for intra-cerebral aneurysm rupture. For a long time, the treatment and management strategies of this disease have not progressed in comparison with the treatment of other kidney

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diseases. Recently, there have been new therapeutic hopes with identification of specific drugs based on the mechanisms of kidney progression. This chapter reviews the treatment and management of ADPKD progression, and the identification of ADPKD patients with rapidly progressing disease, hypertension, and extrarenal complications.

Key words: ADPKD; Chronic kidney disease; Hypertension; Treatment

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening single-gene disease associated with significant morbidity and mortality (1-3). It affects up to 15 million people and represent the 4th most common cause for end-stage kidney disease worldwide (ESKD) (4). ADPKD is a multi-systemic and progressive disorder characterized by cyst formation and enlargement in the kidney and other organs. The natural history of ADPKD was characterized by progressive increase of renal volume and decline of glomerular filtration rate (GFR) (5). Up to 50% of patients with ADPKD require renal replacement therapy by 60 years of age (6). For a long time, the treatment and management strategies of this disease have not been progressed in comparison with the treatment of others kidney diseases. Recently, there have been new therapeutic hopes with identification of specific drugs based on the mechanisms of kidney progression (7). In this chapter, we will summarize the key findings, highlight recent developments, and look ahead to the changes in clinical practice that will likely arise from the adoption of an updated management framework for this major kidney disease.

Management of kidney disease progression in ADPKD

ADPKD progression is highly variable among families and among individuals within families (8), with relative risk of renal decline varying significantly across the population. ADPKD is a significantly heterogeneous disease, making the prediction of progression for a given individual a challenging process. In the absence of reliable and readily available biomarkers and long-term cohort data sets, disease modelling may play a role in defining the wider clinical assessment of at-risk patients and assist in practical decision making (9, 10). Total renal volume is the best predictor of progression of CKD (11).

Vasopressin and the associated cAMP-related signaling pathways have been demonstrated as important contributors for cyst growth in ADPKD, providing rationale for the investigation of vasopressin (V2) receptor antagonism on cystogenesis and proliferation

(12). In 5-year prospective study of Tolvaptan versus placebo, ADPKD patients have been demonstrated a decreased rate of total renal volume growth and a slower decline in kidney function (13). Ensuring that Tolvaptan is used in a safe and effective manner requires multiple considerations, including the careful selection of patients eligible for treatment, based on risk of progression. Patient will need to be supported throughout treatment initiation and long-term management. Japan and the European Medical Agency have approved Tolvaptan for treatment of ADPKD in adults with stage 1 to 3 chronic kidney disease at the outset and evidence of rapidly progressing disease. In the USA, the FDA requested additional data to further evaluate the efficacy and safety of this drug. Identifying ADPKD patients with evidence of rapidly progressing disease requires a consensus to define which scores to use. In addition, results of randomized studies in later stages of ADPKD are not encouraging, which suggests that use of Tolvaptan is not recommended without the additional evidence from large clinical trials.

Hypertension management in ADPKD

Hypertension is a common and serious complication of ADPKD, often occurring in 50% - 70% of ADPKD patients early in the disease, before appearance of renal dysfunction (14, 15). The median age at diagnosis of hypertension in ADPKD is 32 years for males and 34 years for females (16) and occurs at an earlier age in comparison with general population (17). Furthermore, hypertension occurs in 30% of children with ADPKD (18-21). Early and effective treatment of hypertension is very important to decrease the morbidity and mortality of ADPKD patients.

The pathogenesis of hypertension in ADPKD is complex and dependent on many factors that influence each other. Activation of the renin-angiotensin-aldosterone system (RAAS), vascular dysfunction related to ciliopathy, activation of efferent sympathetic nerves, renal handling of sodium and others factors have all been found to be involved in the development of hypertension in ADPKD (22-24). Activation of the RAAS seems to have a major role in the pathogenesis of hypertension in ADPKD patients (25).

In patients with renal disease, the goal is a blood pressure of less than 130/80 mm Hg. In patients with ADPKD we have to adopt this blood pressure target. Hypertension is the most important modifiable risk factor in ADPKD and better blood pressure control allows slowing down the progression of kidney disease (26).

Based on pathogenic data of hypertension in ADPKD patients, the best treatment of this disease is RAAS inhibitors with angiotensin-converting enzyme (ACE) inhibitors or

angiotensin II receptor blockers (ARBs). These agents remain the most recommended drugs to treat hypertension in patients with ADPKD, although studies of the RAAS have not convincingly demonstrated that it plays an important role in the pathogenesis of ADPKD. At the moment, there are not sufficient studies that examined the effect of hypertension control on kidney disease progression and occurrence of cardiovascular events (27). In early stages of ADPKD (28), the dual inhibition of RAAS by combination of ACE inhibitor and ARB did not significantly decrease the rate of total kidney volume growth. Rigorous blood-pressure control was associated with a slower rate of total kidney volume growth in comparison with standard blood pressure control, a greater decline in the left ventricular mass index, and greater reduction in urinary albumin excretion. However, no effect on kidney function was observed. In later stages of ADPKD (29), monotherapy blockade of RAAS with an ACE inhibitor was associated with blood pressure control in ADPKD patients with stage 3 chronic kidney disease. The addition of an ARB did not affect the kidney function progression.

Current published data confirm that patients with ADPKD in the United States (30, 31), Denmark (32) and Great Britain (33) are having a better prognosis. There has been earlier diagnosis, better control of blood pressure, more use of RAAS inhibitors, better preservation of renal function, later onset of ESKD, and better survival. Therefore, early control of hypertension is very important in patients with ADPKD to slow down kidney disease progression and prevent occurrence of cardiovascular events (30-33). The improved survival no doubt involves factors in addition to the better control of blood pressure and preservation of renal function, and this issue therefore needs further study.

Extrarenal complications management

Co-morbidity from extrarenal manifestations is largely confined to adult patients. Hepatic cysts develop later than renal cysts and are rarely found in children. Their prevalence reaches 80% after 60 years of age (34). Most patients remain asymptomatic, with preserved liver function. Females tend to have more cysts and multiple pregnancies and use of estrogen increases cyst size and number. Persistent and severe pain may require cyst decompression. Infection of hepatic cysts is rare and requires antibiotics and sometimes drainage. Medical management using somatostatin analogs has led to significant reduction in liver volume with continued use (35). Epithelial cysts in other organs are infrequently seen. These include pancreas, ovaries, spleen, thyroid, endometrium, seminal vesicle and the epididymis. Along with the progressive cyst development in the kidney and other organs, patients with ADPKD are at increased risk for a variety of vascular abnormalities (36, 37). Intracranial aneurysms have been found in 8% of patients, compared to 1.2% in the

general population, and appear to be clustered in families (1, 38). Rupture of aneurysms is the most serious complication in ADPKD and may account for 7% to 13% of deaths in ADPKD. Management of unruptured aneurysms should be discussed with a multidisciplinary team at an expert center. Aneurysms of the aorta and cardiac valve abnormalities have also been reported (39). It is uncertain whether vascular complications result directly from the genetic defect or merely as a consequence of hypertension and renal failure in these patients. In young children extrarenal manifestations have only rarely been noted.

Urinary tract infections may lead to cyst infection, renal abscesses and sepsis and are considered to be risk factors in progression of renal disease (40). These infections may be difficult to treat. Adequate treatment with antibiotics that can penetrate cyst walls is critical (41). Macroscopic and microscopic hematuria may result from a rupturing cyst and is usually self-limiting. Reduced physical activity may be recommended rarely in cases of protracted bleeding.

Pain from ADPKD, sometimes associated with perinephric hemorrhage, can be treated with analgesics. When the pain persists for more than a few days one must consider the possibility of renal infection, stones or tumor. Pain may also be associated with enlargement of cysts. In such cases some relief may be obtained from percutaneous aspiration or surgical reduction of cysts (42). Renal denervation has been used successfully and could be performed concurrently with cyst decortications (42, 43).

ADPKD progresses to ESKD in approximately 50% of patients at 60 years of age (6). Progression appears to be faster in those who have the PKD1 as opposed to the PKD2 genotype (40). Hypertension and kidney infections are considered most important modifiable risk factors for the development of renal failure and should therefore be adequately treated. A slowdown of the progression to ESKD by early treatment of normotensive patients with ACE inhibitors may be hypothesized, but has not yet been established. Reduction in dietary protein intake has shown disappointing results on slowing progression of renal disease (44).

Earlier onset of chronic kidney disease has been related to a younger age at diagnosis, larger kidneys, episodes of hematuria, proteinuria and multiple pregnancies (40). Understanding predictors for rapid progression of this disease has become increasingly important with the emergence of potential new treatments. Several risk factors influencing kidney disease progression in ADPKD have been identified in the current era. Early emergent markers of ADPKD renal disease progression, specifically, total kidney volume, glomerular hyperfiltration, renal blood flow, uric acid, and urinary molecular markers

Table 1. Management of ADPKD patients (13, 15, 46, 47)

Manifestation	Recommendation
Assess for the presence of risk factors for rapidly progressing disease	• PKD-1 gene mutation; • Male gender; • Young age at diagnosis; • Presence of hypertension, • Hematuria • Proteinuria; • Young age at onset of hypertension • Increased total kidney volume
Reduce hypertension risk	• Lifestyle changes -- Smoking cessation -- Dietary salt restriction -- Moderate alcohol consumption -- Maintain BMI between 18.5 and 24.9 kg/m2 through diet and exercise -- Avoid caffeinated drinks • BP: assess and maintain BP <130 / 80 mmHg with RAAS inhibitors
Slow kidney disease progression	• Lifestyle changes, • Tolvaptan approved for ADPKD adults patients with CKD stage 1 to 3 and evidence of rapidly progressing disease
Assess and manage other renal complications • Chronic kidney disease • Renal pain • Kidney stones • Hematuria • Urinary tract and cyst infection • Large symptomatic cyst	• Monitor eGFR and refer to nephrologist • Symptom review • Maintain adequate fluid intake (3 liters per day) for primary prevention • Reduced physical activity • Antibiotics , fluoroquinolones • Consider avoiding oral contraceptive pill and hormone replacement therapy in women with severe polycystic liver disease • Aspiration and sclerotherapy, • Cyst fenestration, resection
Assess and manage other systemic complications • Intracranial aneurysms	• Consider screening for intracranial cerebral aneurysm in ADPKD patients with high risk • Clipping or endovascular procedure

ADPKD (autosomal dominant polycystic kidney disease); BP (blood pressure); BMI (body mass index); CKD (chronic kidney disease); ESKD (end-stage kidney disease); eGFR (glomerular filtration rate); RAAS (renin-angiotensin-aldosterone system); TVK (Total kidney volume).

have been implicated (9, 10). ADPKD patients with EKRD can be dialyzed and receive renal transplants equally well as patients with most other renal disorders. Patients at-risk for the development of cerebral aneurysms, including those with a positive family history, should be screened by cerebral computed tomography and/or magnetic resonance imaging (45). Asymptomatic at-risk children in ADPKD families are usually followed-up annually for the development of hypertension, hematuria and urinary tract infections. Hypertension and urinary tract infections need prompt and adequate treatment because these may enhance the progression of renal lesions.

Lifestyle modifications, consultations and long-term monitoring in ADPKD

Patients with ADPKD should avoid violent sports. All ADPKD female of reproductive potential should receive counseling on potential aggravation of polycystic liver disease with exogenous estrogen or progesterone exposure. Non-hypertensive ADPKD patients with normal kidney function should undergo blood and urinary testing and ultrasonography of the kidneys every year. ADPKD patients with high blood pressure, chronic kidney disease or cardiovascular complications require more frequent monitoring, based on the severity of hypertension and stage of chronic kidney disease.

ADPKD is the most common hereditary renal disease in the adult. Strategies of treatment and management should be individualized for each ADPKD patient. The objective of this chapter is to provide an update approach and current state of knowledge related to the evaluation, management and treatment of ADPKD (Table 1). Recent recommendations for ADPKD have been published to help with improving disease management and treatment (46, 47).

Conclusion

Improvements in screening and diagnosis of ADPKD have allowed earlier diagnosis of disease, later onset of ESKD and better survival. However, the main and most effective therapy remains control of hypertension. Therefore, early and effective treatment of hypertension is very important to decrease the morbidity and mortality of ADPKD patients. Tolvaptan, a V2 receptor antagonist, was demonstrated to be effective in slowing deterioration of renal function and renal volume growth. Currently, we have new tools and early markers to monitor and detect complications earlier such as total kidney volume. Nephrologists should regularly followed-up ADPKD patients to screen earlier the other complications related to ADPKD for early management.

Conflict of interest

The author declares that he has no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

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