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Case Report

Cardiovascular Phenotype in Patients with Autosomal Dominant Polycystic Kidney Disease: Current State, Screening and Prevention

Rodolfo Fernando Rivera[1]*, Luca Di Lullo[2], Antonio De Pascalis[3], Fulvio Floccari[4], Antonio Bellasi[5], Giancarlo Joli[6], and Maria Teresa Sciarrone Alibrandi[6]

[1]*Department of Nephrology and Dialysis, San Gerardo Hospital, Italy*
[2]*Department of Nephrology and Dialysis, L. Parodi – Delfino Hospital, Italy*
[3]*Department of Nephrology and Dialysis, Vito Fazzi Hospital, Italy*
[4]*Department of Nefrologica e Dialisi, Ospedale San Paolo, Civitavecchia, Italy*
[5]*Department of Nephrology and Dialysis, Sant'Anna Hospital, Italy*
[6]*Department of Nephrology Dialysis and Hypertension, IRCCS San Raffaele Hospital, Italy*

***Corresponding author**
Rodolfo F. Rivera, Department of Nephrology and Dialysis, San Gerardo Hospital, ASST Monza, Italy, Tel: 390-392-334304; Email: rodolfofrivera@gmail.com

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder in nephrology. Two genes have been implicated in the development of the disease: *PKD1* on chromosome 16 (85%) and *PKD2* on chromosome 4 (15%). ADPKD is clinically characterized by renal and extra renal involvement expressed with the onset of cystic and non-cystic manifestations. Since cardiovascular complications are leading cause of morbidity and mortality, this review aims to analyze cardiac and vascular involvement in ADPKD.

Hypertension is a common early symptom, and occurs in approximately 60% of patients before renal dysfunction. The effect of hypertension on the progression to end-stage renal disease makes it the most important potentially treatable risk factor in ADPKD. Left ventricular hypertrophy also occurs frequently in these patients representing another powerful and independent risk factor for cardiovascular morbidity and mortality in ADPKD. Other abnormalities such as biventricular diastolic dysfunction, endothelial dysfunction and increased carotid intima media thickness are present even in young ADPKD patients with normal blood pressure and well-preserved renal function. Intracranial and extra cranial aneurysms and cardiac valvular defects are other common cardiovascular manifestations in patients with ADPKD. Early treatment of hypertension through the use of renin-angiotensin-aldosterone system blocking agents could play a nephroprotective effect and reduce the occurrence of cardiovascular complications in ADPKD patients.

ABBREVIATIONS

ADPKD; Autosomal Dominant Polycystic Kidney Disease; CV: Cardiovascular; BP: Blood Pressure; LVH: Left Ventricular Hypertrophy; LVM: Left Ventricular Mass; RAAS: Renin-Angiotensin-Aldosterone System; PRA: Plasma Renin Activity; NO: Nitric Oxide; DD: Diastolic Dysfunction; PE: Pericardial Effusion; ICA: Intracranial Aneurysms; CKD: Chronic Kidney Disease; MDRD: Modification of Diet in Renal Disease

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disease in nephrology. With an incidence of 1 in 1,000 individuals, this disease is the leading genetic cause of end stage Renal Disease, (ESRD) in adults. Overall, ADPKD represents 4% of the causes of ESRD and usually requires dialysis for 5-10% of patients [1] .

ADPKD is genetically heterogeneous and there are two different types of ADPKD [1,2]. Type I, caused by mutations of the *PKD1* gene on chromosome 16 encoding polycystin-1, is the most common form of PKD and is responsible for 85% of the cases. This is also the most aggressive form and is associated with earlier onset and higher mortality rates. Type II, caused by mutations of the *PKD2* gene on chromosome encoding polycystin-2, is responsible for 10-15% of the cases and is characterized by a slower evolution, which makes it clinically less aggressive than type I. Possible heterozygosity conditions were also described for *PKD1* and *PKD2* mutations. ADPKD is thought to be of complete penetrance, affecting all those who inherited the genetic mutation. It is also characterized by variable expressivity, as its onset may follow different paths and the development of the cysts may vary from one patient to another. This is why affected first-degree relatives should undergo an instrumental and/or

genetic clinical-anamnestic diagnostic screening. Mutation in the *PKD1* and *PKD2* genes, account for the overwhelming majority of ADPKD cases. There are no convincing evidence for the existence of a thir for PKD gene [3]. From the clinical point of view, genetic testing is not a useful screening tool because it can identify only approximately 70% of the hundreds of different *PKD1* and *PKD2* mutations [1,4]. On the basis of effectiveness, cost, and safety, ADPKD is diagnosed through family history (autosomal dominant inheritance) and kidney ultrasound (US) imaging. In a pre-symptomatic at-risk family members the screening is currently based on US age-dependent criteria [5,6]. Specify two or more cysts as diagnostic for individuals ages 15 to 29, two cysts in each kidney for ages 30 to 59, and a minimum of four cysts in each kidney for older at-risk individuals. The finding of fewer than two cysts in each kidney is sufficient to exclude the disease in people who are 30 or older. However, the criteria have been validated only for *PKD1*.

ADPKD may also be mistaken for a kidney disease due to the presence of cysts. It is therefore worth remembering that there are several extra-renal phenotypic manifestations making it a systemic disease. In fact, other organs may be affected by cysts including the liver, the pancreas, the spleen and the thyroid. The disease is also associated with a higher prevalence of colonic diverticula and inguinal hernias than the general population. There are, therefore, several non-renal clinical expressions of ADPKD which are often asymptomatic and potentially responsible for complications [7] (Figure 1).

The cardiovascular (CV) system is also affected by ADPKD. CV system alterations due to ADPKD have become an area of great interest to investigate the effects on renal function and mortality. The first reference to this extra-renal expression was made by Leier et al. [8], in 1984. The cardiac and vascular phenotype of the disease is diverse and is mainly characterized by the presence of early onset of arterial hypertension, due to left ventricular hypertrophy (LVH), and valvular abnormalities [9]. From a vascular point of view, brain [10] and coronary aneurysms [11], thoracic and abdominal aorta aneurysms, endothelium functional alterations and thickened supra-aortic vessels [12] may be observed.

Many of these factors and others such as age, male gender, African race, presence of hematuria, proteinuria, the volume of renal cysts and high blood pressure (BP) have been associated with a rapid decline in kidney function. Among these factors, hypertension is the most frequent and earliest issue, but it can also be easily treated.

This review will address the main issues associated with CV phenotype in ADPKD patients.

Hypertension

Hypertension is the most common clinical manifestation with the greatest impact on renal function in ADPKD patients [13] (Figure 2). Typically the onset of high BP occurs approximately 10 earlier (32-34 years) than in patients with essential hypertension (45-55 years) [14,15]. Hypertension can be observed in 50-70% of ADPKD patients with decreased renal function [16,17]. Elevated BP parameters are more precocious and more common

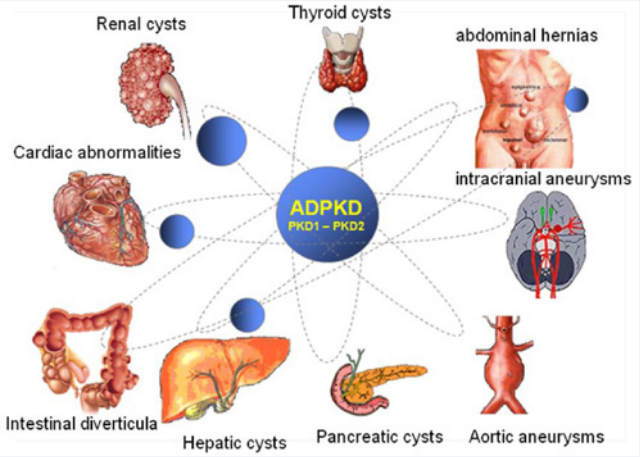

Figure 1 Renal and extra-renal manifestation in autosomal dominant polycystic kidney disease.

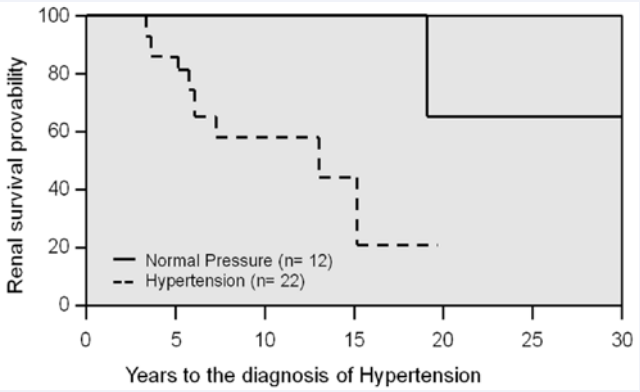

Figure 2 Effects of Blood Pressure on renal survival in ADPKD patients.

in patients with *PKD1* mutation than in those with *PKD2* mutation [15].

Familiarity is an important risk factor for the development of high BP. Children from families with a history of ADPKD has higher BP than control children. In addition, children of ADPKD patients with hypertension are more likely to develop hypertension than those without hypertension [18-21].

The CV risk associated with hypertension in ADPKD patients has two components: elevated BP levels and alterations of the circadian rhythm.

Nocturnal fall in BP, measured by 24-h ambulatory BP monitoring using ascillometric devices, was attenuated in hypertensive ADPKD patients compared with essential hypertensive patients [22]. A more recent study based on hypertensive ADPKD with a stable antihypertensive regimens [23], establishes that the majority of ADPKD patients (56-64%) are non-dippers, independently from renal function, age, duration of hypertension or any other variable considered. Of note, the frequency of non-dipping in essential hypertension [24] is significantly lower (25-42%) than that reported in hypertensive ADPKD population.

For ADPKD patients with hypertension and a non-dipping pattern the CV risk is higher, while the therapeutic correction able to turn a non-dipping into a dipping profile improves the patient's CV prognosis [25].

The mechanisms underlying the genesis of hypertension in patients with ADPKD have not yet been fully elucidated, and currently there are at least three main theories providing a possible explanation.

The first theory concerns the activation of the renin-angiotensin-aldosterone system (RAAS). With the same glomerular filtration rate, ADPKD patients with hypertension show a renal vascular resistance and an increased plasma renin activity (PRA) compared to normotensive ADPKD patients [26]. Moreover, a decrease in mean arterial pressure, renal vascular resistance and filtration fraction induced by angiotensin converting enzyme inhibitor (ACE-I) is more marked in ADPKD patients compared to control patients. The kidney volume seems to play an important role as well. In ADPKD patients with hypertension the renal volume is greater than normotensive ADPKD individuals of the same age [27]. The study conducted by the "Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease" (CRISP) [28], showed that the increase in renal volume is associated with reduced renal blood flow, and this association precedes functional loss.

The second theory is based on the presence of endothelial dysfunction. ADPKD normotensive patients with normal renal function, showed an endothelium-dependent relaxation impairment of the vascular system. Angiotensin II stimulates the production of oxygen radicals that can exert deleterious effects on endothelial integrity. In these subjects, the plasma concentration of nitric oxide (NO) is lower than in control patients [29].

Endothelium-dependent relaxation is also impaired, and endothelial NO synthase activity is reduced in ADPKD patients [30].

The imbalance in endothelium-derived vasoactive mediators such as NO might therefore be an important factor in the pathogenesis of hypertension in ADPKD [31]. It is been speculated that endothelial dysfunction may be primary in the vascular ADPKD phenotype, which includes hypertension but also intracranial aneurysms, atherosclerosis, dissection, edema, hemorrhage and vascular ectasia [32].

The third theory concerns the activation of the sympathetic system. The activation of the sympathetic system has been implicated in the genesis of different forms of hypertension. In ADPKD, change in renal blood flow and intrarenal pressure, and the subsequent production of ischemic metabolites and uremic toxins, continuously stimulate mechanoreceptors and chemoreceptors of renal afferent sensory nerves, contributing to hypertension. ADPKD patients with normal renal function showed higher levels of circulating catecholamines than patients with essential hypertension. Furthermore, BP values are directly associated with the circulating norepinephrine levels, regardless of renal function [33]. A higher muscle sympathetic nervous activity (MSNA) was observed in hypertensive ADPKD compared with normal controls, and MSNA is higher among ADPKD patients with renal dysfunction compared with those with preserved renal function [34].

The described mechanisms do not work independently but seem to share many aspects. The growth of renal cysts affects a situation of intra renal ischemia able to contribute to the genesis of hypertension activating all three mechanisms (Figure 3).

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is a powerful independent risk factor for CV morbidity and mortality in essential hypertension patients [35], and an inverse relationship between left ventricular mass (LVM) and GFR is also known [36]. Cardiac remodeling is an adaptive response to high BP, which is also widely prevalent in this population. Several observational studies and clinical trials have detected the presence of LVH in ADPKD patients [10,22,38-44].

According to Chapman et al. [9], hypertensive ADPKD patients have a prevalence of 48% and this association implies lower renal and overall survival rates. As shown in Figure 4, the author found a significant association between high BP and LVM. Since hypertension and LVH are important CV risk factors for these patients, it is reasonable to consider LVH as a powerful indicator of mortality in patients with ADPKD [38]. Of note [9], LVH was still detected in 23% of normotensive ADPKD individuals. It is worth noting some limitation of this study: ADPKD patients were

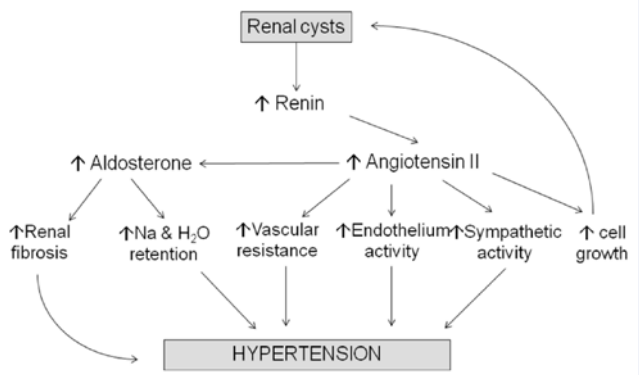

Figure 3 Mechanisms of hypertension in polycystic kidney disease.

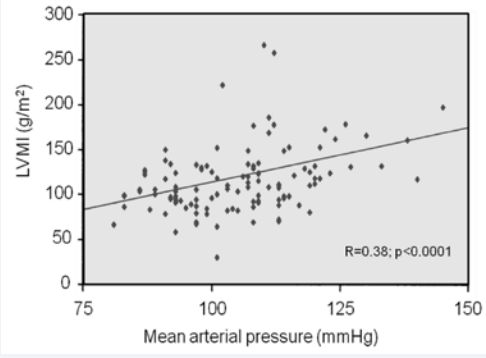

Figure 4 Association between blood pressure and Left Ventricular Mass Index (LVMI) in ADPKD patients.

older, had a higher BP, and had a higher serum creatinine levels than control patients. In addition, there were no any significant difference in US kidney volume, and the authors did highlight that the majority of ADPKD patients in their cohort had inadequate BP control (only two hypertensive ADPKD patients were treated with ACE-I).

Similarly, a Spanish study [40] confirmed the high LVH prevalence in hypertensive ADPKD patients concluding that ambulatory BP is one of the most important determinants of LVM in this population. Nocturnal fall in BP was attenuated in these patients, although it was not associated with the higher LVH that they present. The same group [41] reported no significant difference in plasma renin activity, angiotensin II, aldosterone, noradrenaline, atrial natriuretic peptide, or insulin-like growth factor-1 in hypertensive ADPKD patients with LVH versus those without LVH. Some studies LVH has also was detected even in normotensive ADPKD patients [9,42,43], suggesting that an increase in LVM may precede the onset of hypertension.

As for adults, even for children from families with a history of ADPKD there is a strong correlation between BP and LVM [21,37], and an increase in LVM may precede an increase in renal volume. This is particularly important when evaluating the CV status of these children. A possible limitation of these studies was that kidney volume was estimated by kidney US, rather than direct MR imaging.

Even though many studies are consistent with the high prevalence in LVH in both hypertensive [10,38-42] and normotensive [9,42,43] ADPKD patients, there is not enough available information about the occurrence of LVH separately in *PKD1* or *PKD2* patients for the lack of genotyping. This could represent a serious limitation since patients with *PKD1* mutation seem to have more severe disease than *PKD2* patients [2,44]. In this regard, the only cohort study [39] examining the prevalence of cardiac abnormalities only in type 1 ADPKD, the prevalence of LVH was surprisingly detected in 18.9% (almost half of that found by others authors), which was significantly higher than 5.7% in healthy relatives and 4.2% in healthy, unrelated controls. The prevalence of hypertension across these groups was 71%, 28%, and 14% respectively, of which only 47%, 8% e 0% respectively were under antihypertensive treatment. Once again, the authors found a significant correlation between LVH and higher BP values. However they do not explain the potential factors associated with low LVH prevalence detected in comparison with that reported by others [10,38-42], especially in a hypertensive ADPKD population with more than 50% free of any antihypertensive therapy.

Echocardiography is ready available and more often the procedure of choice for assessing LVH. M-mode (motion based) or Two-dimensional echocardiography with Doppler have been used to direct visualization of the myocardium and real-time quantify the degree of LVH. However, obtaining good quality images is dependent on a skilled operator, patient position and anatomy, thoracic acoustic impedance, and angle of transducer beam, and images of sufficient quality for LVM measurement may not be obtained in up to one third of cases [45]. Echocardiography technique has been utilized in published literature, and this may explain some of the discrepancies observed between studies.

The gold standard for assessing LVM is cardiac magnetic resonance imaging (MRI),which is more accurate for measurement of heart morphology and dimensions and also allows the classification of the pattern of LVH such as concentric or eccentric hypertrophy [46].

The HALT-PKD trial [47], is the largest study population conducted in hypertensive ADPKD, and represents not only the largest cardiac MRI assessment of LVM in ADPKD patients, but also one of the largest cardiac MRI studies in any hypertensive population. The study found an unexpected low prevalence of LVH (less than 4%) as compared to previous study [10,38-42]. According to the authors, multiple factors may explain this finding: 1) the younger age of participants (less than 50 years), 2) almost 60% of participants were already taking RAAS blocker therapy and there were no baseline differences in LVM at the time of study enrollment, and 3) overall better BP control prior to study enrollment, perhaps due to changes in clinical practice towards more strict control. In fact, more aggressive BP control and use of ACE-I ADPKD patients has been associated with regression of LVH [48]. An epidemiological study conducted by Schrier et al. [49], comparing cohorts of subjects studied between 1985-1992 to a latter cohort studied from 1992 to 2001, documented a better BP control (133/82 versus 136/92), which was associated with greater use of ACE-I (54.1% versus 13.1%) and lower use of diuretic (16.1% versus 42.2%) in the later as compared to the early cohort.

The new evidence provided from the HALT-PKD study has modified the widespread awareness that LVH is a common and early manifestation in hypertensive ADPKD. Reduction in BP targets and increased used of RAAS blocking agents could be the causal factors of this unsuspected finding.

Diastolic ventricular dysfunction

The presence of LVH promotes development of a systolic/diastolic cardiac insufficiency. Several authors [50,51] have demonstrated that, in 50– 60% of patients with advanced kidney disease, a diastolic dysfunction (DD) of the left ventricle accompanies its hypertrophy.

In a concentric LVH, the systolic function remains normal while impaired diastolic function represents the earliest sign of cardiac injury. Systolic failure develops a great deal less frequently and is often accompanied by left ventricular distension. In the diagnosis of diastolic dysfunction, an echocardiography examination is of utmost importance because it may demonstrate early-restricted left ventricle diastolic filling with normal systolic function. The earlier affected diastolic function is likely due to the fact that diastole requires more energy for the dissociation of calcium from contractile proteins and for calcium's transport against a concentration gradient to the sarcoplasmic reticulum.

There are few studies investigating the presence of left ventricle DD in patients with ADPKD. In normotensive ADPKD patients with normal renal function, an association between LVH and early DD was observed [52]. In a cohort of ADPKD patients with normal renal function, other authors [53] found that DD was biventricular, both in normotensive and hypertensive patients with ADPKD. However, in a later study [54] that included only young polycystic normotensive patients with normal renal

function, diastolic function was normal, except in cases of DD as a prominent sign of ADPKD. It follows, therefore, that the presence of DD is not a pathognomonic sign of ADPKD but is associated with some risk factors such as the extent of renal injury, patient age and severity of hypertension or LVH. In fact, the same working group [55], found that DD was associated with the progression of kidney disease, patient age and the presence of LVH. However, the lack of a control group limits the results of this study significantly.

DD is a valid parameter of early cardiac damage to be investigated in patients with ADPKD.

Heart valve abnormalities

Heart valve abnormalities are important cardiac manifestations documented in patients with ADPKD. The prevalence of these abnormalities in previous studies has been very variable, and according to the authors, rates range from 25% to 30% [8,53,55]. As for the other clinical manifestations, lack of genotyping of patients into subgroups of ADPKD (*PKD1, PKD2*), and differences in echocardiographic criteria for cardiac valve abnormalities in their studies could be some of the reasons for variable results, which represent an serious limitation [2,44].

Leier et al. [8], observed this phenomenon in 18% of patients and in 27% of autopsy reports. The main defects included aortic root dilation and mitral valve prolapse (Table 1). A retrospective study reported a prevalence of 26% of mitral valve prolapse, 15% of tricuspid regurgitation and 6% of tricuspid prolapse in ADPKD patients [56]. These data were confirmed in a subsequent study conducted by Professor Timio [57], who also reported a high prevalence of cardiac valvular abnormalities. In that report, only one family was studied. Although the family was not genotyped, it seems very likely that those patients had *PKD1*. More recently, the only study that examined cardiac abnormalities only in *PKD1* patients [39], a relatively high prevalence of mitral valve prolapse (25.7%) and mitral regurgitation (12.8%) were further confirmed (Figure 5).

However, Bardaji et al [52], found that the incidence of cardiac valvular abnormalities in normotensive ADPKD patients was similar to that reported in the general population. In the study by Saggar-Malik et al. [42], none of the patients with ADPKD had mitral prolapse, mitral regurgitation, or aortic regurgitation. Ritz et al [58], reported a 17% prevalence of mitral regurgitation in ADPKD patients, however none of the patients had mitral valve prolapse. In these two last studies [42,58], criteria for cardiac valvular abnormalities were not reported, so it is not possible to establish the differences

Also for children from families with a history of ADPKD, a higher prevalence of mitral valve prolapse respect to children from families not affected by ADPKD was observed (12% vs 3%) [21].

In *PKD1* patients [39], the prevalence of mitral valve prolapsed decreased with age, and renal function and systolic BP were not associated with mitral prolapse. The lack of association between mitral prolapse and BP in children and young adults suggests that valve defect is not a secondary phenomenon, but rather a characteristic manifestation of ADPKD.

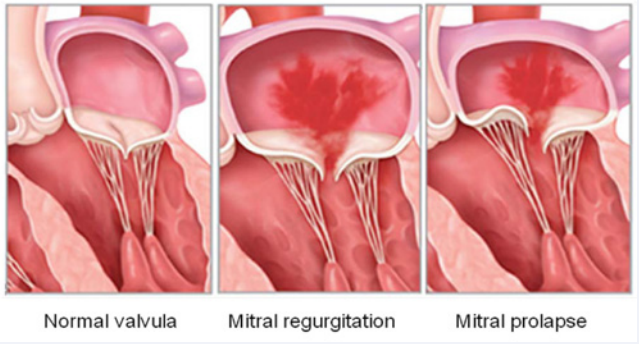

Figure 5 Mitral valve disease in patients with polycystic kidney disease.

Table 1: Frequency of cardiac valve defects in patients with polycystic kidney disease.

Type of heart valve defects	% described
Mitral valve prolapse	26%
Mitral regurgitation	31%
Aortic regurgitation	8%
Tricuspid regurgitation	15%
Tricuspid regurgitation	6%

The cause of heart valve abnormalities is not yet clear, but collagen and extracellular matrix structural alterations may cause this phenomenon. Most patients are clinically asymptomatic and heart murmurs are less frequently detected during the clinical examination than valvular defects detected by echocardiography. However, these lesions may progress over time and require valve replacements, as well as specific monitoring and antibacterial prophylaxis.

Pericardial abnormalities

Pericardial effusion seems to be another cardiovascular phenotype in patients affected by ADPKD (Figure 6). A retrospective analysis conducted at Mayo Clinic [59] detected, by thoracic tomographic, (CT) a higher frequency of pericardial effusion (PE) in patients with ADPKD with an involvement of renal function than in control patients with chronic renal failure (CRF) who were not affected by ADPK and in healthy control subjects. According to those clinical records, the prevalence of PE was 35% in ADPKD patients, 9% in patients with CKD and 4% in healthy controls. Moderate to severe PE was observed in ADPKD patients, not associated with the degree of renal insufficiency. Moreover, it was well tolerated from a clinical point of view. The authors suggest an evaluation of the pericardium in ADPKD patients as a new marker of organ damage. The cause of pericardial effusion is unknown but it is thought to be due to connective tissue alterations caused by ADPKD.

In a cohort of ADPKD patients recently studied by our group [60] the high prevalence of PE detected by echocardiographic was confirmed in patients with ADPKD compared to age and gender-matched controls with the same renal function. Thirty-five percent of ADPKD patients of this cohort showed PE, while the rate for patients not affected by ADPKD was 13.5%. Patients

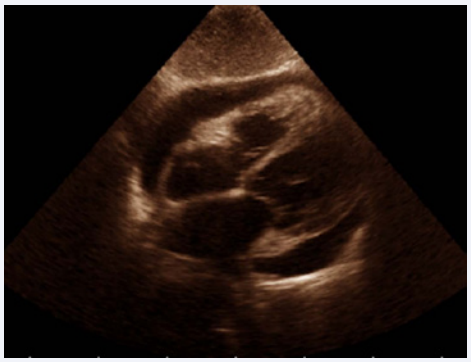

Figure 6 Inferior echocardiographic window showing a Pericardial Effusion in asymptomatic patient with ADPKD.

with PE were as much as 2.8 times more likely to suffer from a CV disease, but without any change in the renal outcome (dialysis). The presence of ADPKD did not increase the CV risk or the need for dialysis, thus suggesting that the presence of PE does not affect the clinical course of the cardiac or the renal phenotype in ADPKD patients. Further clinical studies are required to better understand the role of PE in patients with ADPKD.

Aneurysms

ADPKD is often associated with the presence of aneurysm, which is a weakening of the blood vessel wall, commonly caused by structural abnormalities in arterial wall. Aneurysmal pathology is characterized by increased production and accumulation of matrix proteins between elastin layers, increased proliferation of vascular smooth muscle cells, elastin fragmentation, and ultimately wall thinning potential to cause rupture and hemorrhage [61].

One of the most frequent and dangerous extra-renal manifestations of ADPKD is intracranial aneurysms (ICA), for which the risk of rupture is high. ADPKD patients are more likely to develop ICA than the general population (4-11.7% vs 1-5%) [10]. The ICA prevalence is even higher (approximately 22%) in cases of a positive family history of ICA [62,63].

Usually, ICA are asymptomatic, but their rupture is responsible for 4-7% of deaths of ADPKD patients and, in most cases, they occur at a younger age compared to the general population [63,64]. Normotensive and asymptomatic patients with an ICA less than 10 mm are less likely to develop new aneurysms and the risk of aneurysms enlargement is also low, which is why a conservative treatment is preferred. On the other hand, for patients with an ICA greater than 10 mm or of any other size, the risk of rupture is 3-4% each year, which is why surgical correction or endovascular aneurysm repair are recommended [66]. As for conservative treatments, BP must be kept at a healthy level, while avoiding environmental risks such as smoking, alcohol consumption, stimulant medications and excessive stress [67]. Several studies have emphasized the familial clustering of ruptured ICAs in ADPKD [64, 66], and even if an association between 5 'region of *PKD1* and the increase of ICA was reported [69], large cohort study did not support this finding [70].

There are no randomized, controlled studies assessing the benefit of screening for unruptured ICA in ADPKD patients. Considering the family history distribution of ICA, previous ICA rupture and past events of cerebral hemorrhage, the opinion from clinical experts [10], as well as the KDIGO controversies conference [1], are summarized as follows: no systematic screening of ICA in all ADPKD patients rather targeted screening in patients with a good life expectancy with a known family history of ICA or subarachnoid hemorrhage, patients with previous ICA rupture, those with high risk professions and anxious patients despite adequate information. Use of time-of-flight (TOF) MRI without gadolinium enhancement as the screening method of choice [71], and rescreening at 5–10-year intervals in at-risk patients. However, different opinions have also been published, supporting systematic screening for all patients with ADPKD [72] as well as screening before major elective surgery or renal transplantation.

For ADPKD patients the aneurysmal involvement of extra cranial arteries, such as coronary arteries [11], the abdominal aorta, the renal artery and the splenic artery [73] was also reported. There are few documents on the association between ADPKD and the presence of abdominal aortic aneurysm. Some authors report an incidence of approximately 10% [74], but the few available data do not provide a valid confirmation, suggesting that the same incidence may be due to hypertension or atherosclerosis.

In a recent review, Silverio et al [75], reported 27 cases of aortic dissection in ADPKD patients. In comparison with the general population (from the International Registry of Acute Aortic Dissection), ADPKD patients with aortic dissection are younger and have higher BP. The authors suggest that these characteristics are caused not only for genetically determined structural abnormalities of their blood vessels, but also for the higher prevalence of hypertension.

There are even less data available on coronary aneurysms in these patients. According to the literature, the prevalence is quite varied (13-34%) and studies did not involve control groups, therefore it is not possible to determine whether coronary aneurysms are directly related to the disease or not [11,76].

There are other vascular events reported by ADPKD patients, such as dolichoectasia, elongation and distension of arteries caused by a weakening of the vessel walls, and dissections [67,77]. These abnormalities have an incidence of approximately 2.3-4.6% of the patients and are clinically relevant since they may cause severe complications.

Cardiac phenotype treatments

The treatment of CV complications for ADPKD patients is aimed at achieving two main objectives: slowing the progression of renal failure and preventing CV complications.

To achieve the first objective it is necessary to take into account the important role of the RAAS system in the genesis of hypertension in ADPKD patients. Many authors, in fact, tried to analyze the neuroprotective effects obtained by controlling BP through the use of RAAS blocking agents. Two major clinical trials were conducted in patients with chronic kidney disease (CKD), including ADPKD, to achieve this objective, unfortunately without success.

In the "Modification of Diet in Renal Disease" (MDRD) study, no differences were observed in the progression of renal functional loss between CKD patients treated with aggressive antihypertensive therapy and patients treated with a standard therapy [78], probably because therapeutic targets were not achieved. ADPKD patients included in the study had more severe CKD, a shorter follow-up duration and the type of antihypertensive treatment, the progression of kidney volume and CV events were not considered. Similarly, in the "Angiotensinconverting- enzyme Inhibition in Progressive Renal Insufficiency" (AIPRI) study, the neuroprotective effects induced by ACE-I (benazepril) were greater for patients with glomerular disease or diabetes mellitus compared to ADPKD patients [79], with no improvement in functional impairment. Also in this case, ADPKD patients had more severe CKD and a shorter follow-up duration.

Other randomized studies involving hypertensive patients with ADPKD confirmed the renoprotective effect of RAAS inhibitors, both with ACE-I [80] and with angiotensin receptor blocker ARB [81] compared to the use of calcium antagonists [82] and beta-blockers [83], but not differences were observed in renal function. In a non-randomized retrospective study [84] a greater decline in renal function and more severe proteinuria were associated with the use of diuretics, rather than with the use of ACE-I.

A meta-analysis [85] of eight randomized trials involving 142 ADPKD patients, reported low levels of proteinuria in patients treated with con ACE-I and this effect seems to be proportional to the amount of proteinuria. In this analysis, no difference in the progression of kidney disease between ADPKD patients treated with RAAS blockers and patients treated with other antihypertensive medications were found.

The HALT-PKD (Progression of Polycystic Kidney Disease) is the first prospective randomized double-blind placebo-controlled intervention trial of hypertensive adults with early ADPKD. Actually these are two [86,87] simultaneous multicenter clinical trials designed to test the efficacy of interruption of RAAS on the progression of cystic disease and the decline in renal function in ADPKD. Specifically, the studies test the effects of ACE-I/ARB combination therapy as compared to ACE-I alone in hypertensive ADPKD subjects. The two studies vary on eligibility criteria (particularly kidney function), BP treatment, and primary outcome. Study A [86] investigates treatment effects on individuals with early ADPKD and implements a standard vs. low-BP control target for both treatment arms. Study B [87] investigates treatment effects on moderately advanced ADPKD patients in the setting of standard BP control.

The results of these studies emphasize the potential importance of early detection and aggressive treatment of hypertension in ADPKD. ACE-I alone can adequately control hypertension in over 70% of ADPKD patients, justifying its use as first line treatment for hypertension in this disease. Subjects from low-BP control target group showed significantly lower increase in kidney volume and reduction in urinary albumin excretion, compared to those from standard-BP control target group. The overall effect of low-BP control on renal function, however, was not statistically significant, possibly because an acute reduction in eGFR within the first four months of treatment induced by very low BP levels. Finally, the addition of an ARB to an ACE-I in ADPKD patients with good kidney function or with moderately-impaired renal function, was safe but did not confer any additional benefit. This study demonstrates that dual RAAS blockade is not more efficacious than single blockade even in hypertensive ADPKD patients.

Another objective of the treatment of CV risk factors in ADPKD patients should be the prevention of CV complications.

Blocking the RAAS with ACE-I seem to be effective in reducing LVH at 7 years of follow-up, with a reduced risk of CV death in patients with ADPKD [88]. Other studies showed significant reduction of LVH with the use of RAAS blockers compared to the use of calcium-channel blockers, with the same blood level parameters [48]. In the 7-year randomized trial the authors compared the effects on LVH in hypertensive ADPKD patients undergoing aggressive antihypertensive treatment compared to a standard treatment. Both antihypertensive strategies resulted in a significant reduction in LVH, but better results were achieved for the group undergoing aggressive antihypertensive treatment (71% vs 44%). For a subset of patients from the same study treated with ACE-I, greater LVH regression was observed compared to patients treated with calcium-channel blockers. Also the HALT-PKD study [86], although presenting a low LVH prevalence, has documented the benefit of the low-BP regime on the regression of LVH.

Therefore, the use of ACE-I and a low-BP profile are strongly recommended to prevent LVH in ADPKD patients.

CONCLUSION

CV abnormalities are common in patients with ADPKD. Hypertension is the most common risk factor and it often causes renal and CV complications. LVH is very common in ADPKD patients, which is associated with hypertension and CV mortality. However, the HALT-PKD found an unexpectedly low prevalence of LVH, provably as a result of a better and widespread BP control of hypertensive ADPKD patients early treated.

Other abnormalities, such cerebral and abdominal aneurysms, valvular defects, ventricular diastolic dysfunction, and the presence of pericardial effusion are all manifestations of the cardiac and vascular phenotype of ADPKD.

Early diagnosis and timely treatment with RAAS inhibitors could marginalize the extent of the cardiac organ damage could reduce heart damage, while strict BP control may improve CV prognosis for these patients.

REFERENCES

1. Chapman AB, Devuyst O, Eckardt K-U, Gansevoort RT, Harris T, Horie S, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2015; 88: 17-27.

2. Hateboer N, V Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet. 1999; 353: 103-107.

3. Paul BM, Consugar MB, Ryan Lee M, Sundsbak JL, Heyer CM, Rossetti S,

et al. Evidence of a third ADPKD locus is not supported by re-analysis of designated PKD3 families. Kidney Int. 2014; 85: 383-392.

4. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med. 2008; 359: 1477-1485.

5. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet. 1994 2; 343: 824-827.

6. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009; 20: 205-212.

7. Luciano RL, Dahl NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): considerations for routine screening and management. Nephrol Dial Transplant. 2014; 29: 247-254.

8. Leier CV, Baker PB, Kilman JW, Wooley CF. Cardiovascular abnormalities associated with adult polycystic kidney disease. Ann Intern Med. 1984; 100: 683-688.

9. Chapman AB, Johnson AM, Rainguet S, Hossack K, Gabow P, Schrier RW. Left ventricular hypertrophy in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1997; 8: 1292-1297.

10. Chapman AB, Rubinstein D, Hughes R, Stears JC, Earnest MP, Johnson AM, et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. N Engl J Med. 1992; 327: 916-920.

11. Hadimeri H, Lamm C, Nyberg G. Coronary aneurysms in patients with autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1998; 9: 837-841.

12. Bardají A, Martinez-Vea A, Valero A, Gutierrez C, Garcia C, Ridao C, et al. Cardiac involvement in autosomal-dominant polycystic kidney disease: a hypertensive heart disease. Clin Nephrol. 2001; 56: 211-220.

13. Iglesias CG, Torres VE, Offord KP, Holley KE, Beard CM, Kurland LT. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935-1980. Am J Kidney Dis. 1983; 2: 630-639.

14. Kelleher CL, McFann KK, Johnson AM, Schrier RW. Characteristics of hypertension in young adults with autosomal dominant polycystic kidney disease compared with the general U.S. population. Am J Hypertens. 2004; 17: 1029-1034.

15. Schrier RW, Johnson AM, McFann K, Chapman AB. The role of parental hypertension in the frequency and age of diagnosis of hypertension in offspring with autosomal-dominant polycystic kidney disease. Kidney Int. 2003; 64: 1792-1799.

16. Chapman AB, Schrier RW. Pathogenesis of hypertension in autosomal dominant polycystic kidney disease. Semin Nephrol. 1991; 11: 653-660.

17. Ecder T, Schrier RW. Hypertension in autosomal-dominant polycystic kidney disease: early occurrence and unique aspects. J Am Soc Nephrol. 2001; 12: 194-200.

18. Sedman A, Bell P, Manco-Johnson M, Schrier R, Warady BA, Heard EO, et al. Autosomal dominant polycystic kidney disease in childhood: a longitudinal study. Kidney Int. 1987; 31: 1000-1005.

19. Shamshirsaz AA, Reza Bekheirnia M, Kamgar M, Johnson AM, McFann K, Cadnapaphornchai M, et al. Autosomal-dominant polycystic kidney disease in infancy and childhood: progression and outcome. Kidney Int. 2005; 68: 2218-2224.

20. Fick GM, Duley IT, Johnson AM, Strain JD, Manco-Johnson ML, Gabow PA. The spectrum of autosomal dominant polycystic kidney disease in children. J Am Soc Nephrol. 1994; 4: 1654-1660.

21. Ivy DD, Shaffer EM, Johnson AM, Kimberling WJ, Dobin A, Gabow PA. Cardiovascular abnormalities in children with autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1995; 5: 2032-2036.

22. Li Kam Wa TC, Macnicol AM, Watson ML. Ambulatory blood pressure in hypertensive patients with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 1997; 12: 2075-2080.

23. Rahbari-Oskoui FF, Miskulin DC, Hogan MC, Fielder O, Torres VE, Bost JE, et al. Short-term reproducibility of ambulatory blood pressure monitoring in autosomal dominant polycystic kidney disease. Blood Press Monit. 2011; 16: 47-54.

24. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension. 2001; 38: 852-857.

25. Handa SP. Cardiovascular manifestations of autosomal dominant polycystic kidney disease in young adults. Clin Invest Med. 2006; 29: 339-346.

26. Chapman AB, Johnson A, Gabow PA, Schrier RW. The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. N Engl J Med. 1990; 323: 1091-1096.

27. Schrier RW, Brosnahan G, Cadnapaphornchai MA, Chonchol M, Friend K, Gitomer B, et al. Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol. 2014; 25: 2399-2418.

28. Torres VE, King BF, Chapman AB, Brummer ME, Bae KT, Glockner JF, et al. Magnetic resonance measurements of renal blood flow and disease progression in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol CJASN. 2007; 2: 112-120.

29. Clausen P, Feldt-Rasmussen B, Iversen J, Lange M, Eidemak I, Strandgaard S. Flow-associated dilatory capacity of the brachial artery is intact in early autosomal dominant polycystic kidney disease. Am J Nephrol. 2006; 26: 335-339.

30. Wang D, Iversen J, Wilcox CS, Strandgaard S. Endothelial dysfunction and reduced nitric oxide in resistance arteries in autosomal-dominant polycystic kidney disease. Kidney Int. 2003; 64: 1381-1388.

31. Merta M, Reiterová J, Rysavá R, Tesar V, Závada J, Jáchymová M, et al. Role of endothelin and nitric oxide in the pathogenesis of arterial hypertension in autosomal dominant polycystic kidney disease. Physiol Res. 2003; 52: 433-437.

32. Nauli SM, Jin X, Hierck BP. The mechanosensory role of primary cilia in vascular hypertension. Int J Vasc Med. 2011; 2011: 376281.

33. Cerasola G, Vecchi M, Mulè G, Cottone S, Mangano MT, Andronico G, et al. Sympathetic activity and blood pressure pattern in autosomal dominant polycystic kidney disease hypertensives. Am J Nephrol. 1998; 18: 391-398.

34. Klein IH, Ligtenberg G, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension. J Am Soc Nephrol. 2001; 12: 2427-2433.

35. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991; 114: 345-352.

36. Perticone F, Maio R, Ruberto C, Cassano S, Tripepi G, Perticone M, et al. Kidney function and risk factors for left ventricular hypertrophy in untreated uncomplicated essential hypertension. Am J Kidney Dis. 2008; 52: 74-84.

37. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. Kidney Int. 2008; 74: 1192-1196.

38. Remppis A, Ritz E. Cardiac problems in the dialysis patient: beyond coronary disease. Semin Dial. 2008; 21: 319-325.

39. Lumiaho A, Ikäheimo R, Miettinen R, Niemitukia L, Laitinen T, Rantala A, et al. Mitral valve prolapse and mitral regurgitation are common in patients with polycystic kidney disease type 1. Am J Kidney Dis. 2001; 38: 1208-1216.

40. Valero FA, Martinez-Vea A, Bardají A, Gutierrez C, Garcia C, Richart C, et al. Ambulatory blood pressure and left ventricular mass in normotensive patients with autosomal dominant polycystic kidney disease. J Am Soc Nephrol JASN. 1999; 10: 1020-1026.

41. Martinez-Vea A, Valero FA, Bardaji A, Gutierrez C, Broch M, Garcia C, et al. Left ventricular hypertrophy in hypertensive patients with autosomal dominant polycystic kidney disease: influence of blood pressure and humoral and neurohormonal factors. Am J Nephrol. 2000; 20: 193-200.

42. Saggar-Malik AK, Missouris CG, Gill JS, Singer DR, Markandu ND, MacGregor GA. Left ventricular mass in normotensive subjects with autosomal dominant polycystic kidney disease. BMJ. 1994; 309: 1617-1618.

43. Zeier M, Geberth S, Schmidt KG, Mandelbaum A, Ritz E. Elevated blood pressure profile and left ventricular mass in children and young adults with autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1993; 3: 1451-1457.

44. Torra R, Badenas C, Darnell A, Nicolau C, Volpini V, Revert L, et al. Linkage, clinical features, and prognosis of autosomal dominant polycystic kidney disease types 1 and 2. J Am Soc Nephrol. 1996; 7: 2142-2151.

45. Devereux RB, Casale PN, Wallerson DC, Kligfield P, Hammond IW, Liebson PR, et al. Cost-effectiveness of echocardiography and electrocardiography for detection of left ventricular hypertrophy in patients with systemic hypertension. Hypertension. 1987; 9: 69-76.

46. Di Lullo L, Gorini A, Rivera R, De Pascalis A, Bellasi A, Russo D, et al. [Cardiac magnetic resonance and uremic cardiomyopathy]. G Ital Nefrol. 2014; 31.

47. Perrone RD, Abebe KZ, Schrier RW, Chapman AB, Torres VE, Bost J, et al. Cardiac magnetic resonance assessment of left ventricular mass in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol CJASN. 2011; 6: 2508-2515.

48. Schrier R, McFann K, Johnson A, Chapman A, Edelstein C, Brosnahan G, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. J Am Soc Nephrol JASN. 2002; 13: 1733-1739.

49. Schrier RW, McFann KK, Johnson AM. Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease. Kidney Int. 2003; 63: 678-685.

50. Kunz K, Dimitrov Y, Muller S, Chantrel F, Hannedouche T. Uraemic cardiomyopathy. Nephrol Dial Transplant. 1998; 13: 39-43.

51. Parfrey PS. Cardiac disease in dialysis patients: diagnosis, burden of disease, prognosis, risk factors and management. Nephrol Dial Transplant. 2000; 15: 58-68.

52. Bardají A, Vea AM, Gutierrez C, Ridao C, Richart C, Oliver JA. Left ventricular mass and diastolic function in normotensive young adults with autosomal dominant polycystic kidney disease. Am J Kidney Dis. 1998; 32: 970-975.

53. Oflaz H, Alisir S, Buyukaydin B, Kocaman O, Turgut F, Namli S, et al. Biventricular diastolic dysfunction in patients with autosomal-dominant polycystic kidney disease. Kidney Int. 2005; 68: 2244-2249.

54. Almeida EAF de, Oliveira EI de, Lopes JA, Almeida AG, Prata MM. Tissue Doppler imaging in the evaluation of left ventricular function in young adults with autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2006; 47: 587-592.

55. de Almeida EAF, de Oliveira EI, Lopes JA, Almeida AG, Lopes MG, Prata MM. Diastolic function in several stages of chronic kidney disease in patients with autosomal dominant polycystic kidney disease: a tissue Doppler imaging study. Kidney Blood Press Res. 2007; 30: 234-239.

56. Hossack KF, Leddy CL, Johnson AM, Schrier RW, Gabow PA. Echocardiographic findings in autosomal dominant polycystic kidney disease. N Engl J Med. 1988; 319: 907-912.

57. Timio M, Monarca C, Pede S, Gentili S, Verdura C, Lolli S. The spectrum of cardiovascular abnormalities in autosomal dominant polycystic kidney disease: a 10-year follow-up in a five-generation kindred. Clin Nephrol. 1992; 37: 245-251.

58. Ritz E, Zeier M, Schneider P, Jones E. Cardiovascular mortality of patients with polycystic kidney disease on dialysis: is there a lesson to learn? Nephron. 1994; 66: 125-128.

59. Qian Q, Hartman RP, King BF, Torres VE. Increased occurrence of pericardial effusion in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2007; 2: 1223-1227.

60. Rivera RF, Di Lullo L, Floccari F, Casati C, Grassi M, Stella A, et al. Pericardial effusion and autosomic dominant polycystic kidney disease with different staged of chronic kidney disease. A multicentric cohort study. Congress of American Society of Nephrology, Philadelphia. 2014.

61. Drummond IA. Polycystins, focal adhesions and extracellular matrix interactions. Biochim Biophys Acta. 2011; 1812: 1322-1326.

62. Xu HW, Yu SQ, Mei CL, Li MH. Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. Stroke. 2011; 42: 204-206.

63. Irazabal MV, Huston J, Kubly V, Rossetti S, Sundsbak JL, Hogan MC, et al. Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol CJASN. 2011; 6: 1274-1285.

64. Fick GM, Johnson AM, Hammond WS, Gabow PA. Causes of death in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1995; 5: 2048-2056.

65. Chauveau D, Pirson Y, Verellen-Dumoulin C, Macnicol A, Gonzalo A, Grünfeld JP. Intracranial aneurysms in autosomal dominant polycystic kidney disease. Kidney Int. 1994; 45: 1140-1146.

66. Gibbs GF, Huston J, Qian Q, Kubly V, Harris PC, Brown RD, et al. Follow-up of intracranial aneurysms in autosomal-dominant polycystic kidney disease. Kidney Int. 2004; 65: 1621-1627.

67. Schievink WI, Torres VE, Wiebers DO, Huston J. Intracranial arterial dolichoectasia in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1997; 8: 1298-1303.

68. Belz MM, Hughes RL, Kaehny WD, Johnson AM, Fick-Brosnahan GM, Earnest MP, et al. Familial clustering of ruptured intracranial aneurysms in autosomal dominant polycystic kidney disease. Am J Kidney. 2001; 38: 770-776.

69. Rossetti S, Chauveau D, Kubly V, Slezak JM, Saggar-Malik AK, Pei Y, et al. Association of mutation position in polycystic kidney disease 1 (PKD1) gene and development of a vascular phenotype. Lancet. 2003; 361: 2196-2201.

70. Cornec-Le Gall E, Audrézet MP, Chen JM, Hourmant M, Morin MP, Perrichot R, et al. Type of PKD1 mutation influences renal outcome in

ADPKD. J Am Soc Nephrol. 2013; 24: 1006-1013.

71. Gibbs GF, Huston, Bernstein MA, Riederer SJ, Brown RD. 3.0-Tesla MR angiography of intracranial aneurysms: comparison of time-of-flight and contrast-enhanced techniques. J Magn Reson Imaging. 2005; 21: 97-102.

72. Rozenfeld MN, Ansari SA, Shaibani A, Russell EJ, Mohan P, Hurley MC. Should Patients with Autosomal Dominant Polycystic Kidney Disease Be Screened for Cerebral Aneurysms? Am J Neuroradiol. 2014; 35: 3-9.

73. Torra R, Nicolau C, Badenas C, Brú C, Pérez L, Estivill X, et al. Abdominal aortic aneurysms and autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1996; 7: 2483-2486.

74. Chapman JR, Hilson AJ. Polycystic kidneys and abdominal aortic aneurysms. Lancet. 1980; 1: 646-647.

75. Silverio A, Prota C, Di Maio M, Polito MV, Cogliani FM, Citro R, et al. Aortic dissection in patients with autosomal dominant polycystic kidney disease: a series of two cases and a review of the literature. Nephrol Carlton Vic. 2015; 20: 229-235.

76. Swan SK, Kramer MD, Henry TD, Collins AJ, Herzog CA. Increased incidence of coronary artery aneurysms in patients with autosomal dominant polycystic kidney disease. J Am Soc Nephrol JASN. 1994; 5: 653.

77. Graf S, Schischma A, Eberhardt KE, Istel R, Stiasny B, Schulze BD. Intracranial aneurysms and dolichoectasia in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2002; 17: 819-823.

78. Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol JASN. 1995; 5: 2037-2047.

79. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996; 334: 939-945.

80. Chapman AB, Johnson AM, Gabow PA, Schrier RW. Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994; 5: 1349-1354.

81. Nutahara K, Higashihara E, Horie S, Kamura K, Tsuchiya K, Mochizuki T, et al. Calcium channel blocker versus angiotensin II receptor blocker in autosomal dominant polycystic kidney disease. Nephron Clin Pract. 2005; 99:18-23.

82. Ecder T, Chapman AB, Brosnahan GM, Edelstein CL, Johnson AM, Schrier RW. Effect of antihypertensive therapy on renal function and urinary albumin excretion in hypertensive patients with autosomal dominant polycystic kidney disease. Am J Kidney Dis Off J Natl Kidney Found. 2000; 35: 427-432.

83. Van Dijk MA, Breuning MH, Duiser R, van Es LA, Westendorp RG. No effect of enalapril on progression in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2003; 18: 2314-2320.

84. Ecder T, Edelstein CL, Fick-Brosnahan GM, Johnson AM, Chapman AB, Gabow PA, et al. Diuretics versus angiotensin-converting enzyme inhibitors in autosomal dominant polycystic kidney disease. Am J Nephrol. 2001; 21: 98-103.

85. Jafar TH, Stark PC, Schmid CH, Strandgaard S, Kamper AL, Maschio G, et al. The effect of angiotensin-converting-enzyme inhibitors on progression of advanced polycystic kidney disease. Kidney Int. 2005; 67: 265-271.

86. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al. Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2014; 371: 2255–2266.

87. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. N Engl J Med. 2014; 371: 2267-2276.

88. Ecder T, Edelstein CL, Chapman AB, Johnson AM, Tison L, Gill EA, et al. Reversal of left ventricular hypertrophy with angiotensin converting enzyme inhibition in hypertensive patients with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 1999; 14: 1113-1116.

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