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A comprehensive review of extrarenal manifestations of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Abstract:

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, primarily caused by mutations in the PKD1 and PKD2 genes. It is characterized by the progressive growth of numerous cysts in both kidneys, leading to renal failure. Beyond renal manifestations, ADPKD is associated with a wide spectrum of systemic complications, posing a significant clinical challenge and requiring comprehensive care.

Aim: The aim of this paper was a comprehensive literature review regarding the extrarenal manifestations of autosomal dominant polycystic kidney disease (ADPKD), including their epidemiology, pathophysiology, and clinical significance.

Materials and Methods: The review included scientific papers sourced from the PubMed and Google Scholar databases.

Results: The most common extrarenal manifestation is autosomal dominant polycystic liver disease (ADPLD), with a prevalence reaching 94% in patients over 35; its development is strongly linked to extragenetic factors, mainly estrogen exposure. Cardiovascular manifestations are common and include hypertension (resulting, among other things, from RAAS activation), an increased frequency of aortic dilatation and aneurysms (44% of patients

in one study), which raises the risk of dissection. Left ventricular hypertrophy (LVH) and valvular defects, especially mitral valve prolapse, are also frequent. Intracranial aneurysms (ICAs) occur in 9-12% of ADPKD patients (vs 3% in the general population), and their rupture tends to occur at a younger age. The most significant risk factor for ICAs is a positive family history.

Conclusions: ADPKD is a multisystemic disease, not just a renal one. The wide range of extrarenal manifestations, including hepatic, cardiovascular, and cerebrovascular complications, highlights the necessity for comprehensive screening and the implementation of holistic patient care to identify, assess, and treat all health problems associated with this disease.

Key words: ADPKD, autosomal dominant polycystic kidney disease, ADPLD, ADPKD extrarenal manifestations, ADPKD liver cysts

Introduction:

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. The prevalence of this disease differs depending on the population studied. In total it is estimated to affect over 10 million people worldwide (Bergmann et al., 2019). A nationwide survey performed by Chin et al. between 2009 and 2019 in Taiwan found the prevalence of ADPKD to be 1,26-1,57% (Chin et al., 2024). Another large study carried out in Minnesota by Iglesias et al. suggested the incidence to be 2,75/100 000 people per year (Iglesias et al., 1983). In 2016 researchers reviewed the literature on epidemiology of ADPKD in the European Union published between 1980 and 2015 including data from 19 European countries. The conclusion drawn was that the incidence of ADPKD is 1 in 2,525. (Wiley et al., 2017).

The condition is most often caused by mutations of the PKD1 gene located on chromosome 16p13.3; and the PKD2 gene located on chromosome 4q21. PKD1 encodes a glycoprotein called polycystin-1 (PC1), which is cleaved at a G protein-coupled receptor proteolytic site. PKD2 produces polycystin-2 (PC2), a protein which is a transient receptor of calcium-regulated cation channels. (Cornec-Le Gall et al., 2019). There is a high allelic heterogeneity in patients affected by the condition. A 2016 study by Carrera et al. carried out on an Italian cohort of 440 unrelated patients with ADPKD and 203 relatives found that in in 301 (85.5%) patients the disease was associated with PKD1, 196 (55.7%) truncating, 81 (23%) non truncating, 24 (6.8%) IF indels, and in 51 (14.5%) with PKD2. (Carrera et al., 2016).

Patients suffering from ADPKD develop a number of renal cysts which start to form as early as in utero. Cysts usually form in the distal regions of the nephron and the collecting duct. However they can originate from all areas of the kidneys. (Bergmann et al., 2019). The disease is usually diagnosed in adulthood due to the growing nature of the cysts. In comparison to single benign renal cysts which are common in both children and adults, kidneys in patients suffering from ADPKD contain multiple cysts located bilaterally. In addition to the renal presentation of

the disease a number of complications arise from other systems. This includes an increased risk of developing liver cysts, pancreatic cysts, abdominal hernias, intracranial aneurysms as well as cardiovascular presentation in the form of hypertension, left ventricular hypertrophy, aortic dilatation and valvular diseases. (Hogan et al., 2015; Sanchis et al., 2019; Ong et al., 2015).

The wide range of extrarenal manifestations of the condition highlights the need for a comprehensive screening of patients diagnosed with ADPKD in order to identify, assess and possibly treat every health problem a patient may have in connection with this disease. Currently the only drug proven to modify the prognosis of patients with ADPKD is tolvaptan. (Torres et al., 2012). There are however other options for intervention addressing specific extrarenal manifestations.

Research materials and methods

A comprehensive literature review was conducted using the PubMed and Google Scholar databases. The search focused on systematic reviews, meta-analyses, and key clinical trials published on the topic of autosomal dominant polycystic kidney disease. To cover all relevant aspects, the search strategy included keywords such as "autosomal dominant polycystic kidney disease" "ADPKD" "ADPKD extrarenal manifestations", "ADPKD intracranial aneurysm" and "autosomal dominant polycystic liver disease", "ADPKD cardiovascular manifestations" , "ADPKD aortic dilatation".

Liver cysts:

The most common extrarenal manifestation of autosomal dominant polycystic kidney disease (ADPKD) is autosomal dominant polycystic liver disease (ADPLD). It is estimated that the prevalence of ADPLD reaches almost 85% of patients diagnosed with ADPKD by the time they reach 30 years of age (Muto et al., 2019) growing to even 94% by the age of 35-46 (Amura et al., 2008). Although both genders are affected by the hepatic manifestation of the disease, women have a higher prevalence and severity of the disease, which is believed to be a result of higher exposure to estrogen (Sherstha et al., 1997). It has been proven that pregnancies, oral contraceptive medication and estrogen replacement therapy accelerates the development of the disease (Petrone et al., 2024). Therefore, the main risk factors for developing ADPLD include the female gender, estrogen exposure (multiple pregnancies, oral contraceptive therapy, estrogen replacement therapy), advancing patient's age and severity of renal dysfunction and renal cyst volume (Abu-Wasel et al., 2013). The type of mutation (PKD1 or PKD2) is of no relationship to the severity of the hepatic cysts (Roediger et al., 2022), however, it has been proven that the PKD1 mutation plays a role in earlier onset of the disease in comparison to PKD2 mutation, with a protein encoded by PKD1 gene - polycystin-1 (PC-1), playing a role in cyst formation (Kataoka et al., 2021).

Although autosomal dominant polycystic liver disease (ADPLD) is a manifestation of ADKPD, the formation of cysts in kidneys is impacted by different factors than in the liver. The cyst formation in the kidneys has been clearly linked to the PKD1 and PKD2 mutations, and while those mutations play a role in determining earlier or later onset of liver cysts (Kataoka et al., 2021), they do not affect the severity of polycystic liver disease (PLD)(Roediger et al., 2022). The formation of liver cysts is attributed mostly to extragenetic factors, mainly estrogen exposure, which has become more common. Gynecologists often recommend estrogen supplementation as a method of contraception and managing symptoms of different conditions, including polycystic ovary syndrome (PCOS) despite non-hormonal ways being effective. This phenomenon led to the discovery that female patients with ADPKD who have not taken any

form of estrogen supplementation tend to have a more mild and slower-progressing form of the disease in comparison to patients who have taken estrogen (Sherstha et al., 1997).

Other factors that have been attributed to promoting cyst growth include cytokines and growth factors. Recent studies show that the fluids found in liver and kidney cysts present different factors of accumulation. IL-1, IL-2, TNF-alpha and EGF have been reported to accumulate in kidney cysts, whereas liver cyst fluid contains higher concentration of CXR2 agonists (IL-8, GRO-alpha, ENA-78) and VEGF. It has been hypothesised that IL-8 present in high levels in liver cysts, apart from its well known role in angiogenesis, metastases and promotion of epithelial cell proliferation, might contribute to transepithelial neutrophil migration, however it has not yet been determined with certainty (Amura et al., 2008).

Patients with autosomal dominant polycystic liver disease (ADPLD) are usually asymptomatic and the liver cysts are found during radiological imaging (Roediger et al., 2022). Most of the currently available liver tests do not indicate any signs of dysfunction. The only two tests that have been proven useful in diagnosing the presence of liver cysts include GGT (which in over half of the patients can reach 1,4 times the upper limit of normal) and alkaline phosphatase (which is mildly elevated in around 20% of the patients. The levels of GGT and alkaline phosphatase do not correlate with the severity of the disease (Roediger et al., 2022) .
As the cysts grow, the enlarged liver might exert a mass effect on the surrounding organs, which can in turn cause symptoms. About 20% of the patients might experience abdominal distension, dyspnea, early satiety and gastroesophageal reflux (Roediger et al., 2022). Some of the less common symptoms also include hepatic venous-outflow obstruction (Budd-Chiari syndrome), inferior vena cava syndrome, portal vein compression and bile duct compression (Abu-Wasel et al., 2013) .

The complications do not occur often and they include haemorrhage, infection and rupture. They might be caused by abdominal trauma or by rapid growth. Infections only happen in 1% of the cases and have a mortality rate of 2%. The main symptom that might suggest a complication is acute abdominal pain in the right upper quadrant, others, suggesting infection, apart from pain include fevers and malaise (Roediger et al., 2022; Abu-Wasel et al., 2013) .

Vascular and Cardiovascular Manifestations of ADPKD:

Although primarily affecting the kidneys, ADPKD has a wide range of implications on the cardiovascular system. Researchers agree on the fact that polycystic genes are expressed not only in renal tissue but also in many vascular tissues (Kuo et al., 2019). This in addition to cardiovascular diseases themselves being among the most common conditions affecting people worldwide, makes those manifestations crucial in the holistic care of patients suffering from ADPKD.

The onset of hypertension in ADPKD patients has been widely linked to the RAAS system which plays a crucial role in the regulation of the blood pressure as well as its treatment in most patients irrespective of having ADPKD. Patients suffering from ADPKD have an increased activity of RAAS. That is due to the fact that growing renal cysts impose pressure on the renal tissues. This in turn leads to nephron obstruction and ischemia caused by the obstruction of microvasculature (Oto et al., 2024). Another factor is the modified activity of the polycystin-1 (PC-1) and polycystin-2 (PC-2) proteins themselves. Their altered activity causes lowered calcium levels and increased cyclic adenosine monophosphate, thus disrupting the intracellular signaling pathways (Vasileva et al., 2021). Since PC-1 and PC-2 were also found to be expressed in the vascular tissue, this altered function has its implications on the blood vessels. Both the vascular structure and function are affected by means of reduced nitric oxide

levels (a molecule which acts as a relaxing agent on blood vessels) and impaired endothelial function leading to its increased constriction (Oto et al., 2024).

Another cardiovascular manifestation of ADPKD was found to be aortic dilatation and consequently aortic aneurysm. A 2018 study by Bouleti et al. focused on the prevalence of aortic dilatation and ascending aortic aneurysms in ADPKD patients. The researchers looked at echocardiography data from 61 patients suffering from the condition and compared them to control group matching by similar age, sex, blood pressure and beta-bloker therapy. It was discovered that the Sinuses of Valsalva (SoV) diameters were significantly larger in ADPKD patients than in the control group (36.4±4.4 versus 34.0±3.7 mm, $p<0.0001$). Moreover, aortic aneurysms, as defined by a Z-score>2 standard deviations were present in 27 ADPKD patients (44%) versus 9 controls (15%, $p<0.001$). (Bouleti et al., 2018). Another study by Savis et al. focusing on aortic dilatation in 97 children and young people with ADPKD also proves an increased incidence of this vascular manifestation. This study included measurements from 4 locations: namely the aortic valve annulus, sinuses of Valsalva (SoV), sinotubular junction (STJ), and the ascending aorta. The prevalence of dilatation in the trial group ranged from 5.2% to 17% depending on the location, while there was no aortic dilatation identified in the control group. Moreover, in multivariable regression analysis, aortic root dilatation was significantly associated with cyst burden at the aortic valve annulus and SoV ($\beta= 0.42$ and $\beta= 0.39$, both $P < 0.001$), with age at SoV ($\beta=-0.26$, $p< 0.02$), systolic blood pressure (SBP) z-score at SoV ($\beta= -0.20$, $p= 0.04$) and left ventricular mass index (LVMI) at SoV and STJ ($\beta= 0.24$, $p=0.02$ and $\beta= 0.25$, $p= 0.03$, respectively) following adjustment for age, sex (male or female), body mass index (BMI) z-score, estimated glomerular filtration rate (eGFR), SBP z-score, and LVMI (Savis et al, 2024).

Aortic dissection poses a very dangerous, yet quite prevalent complication of aortic aneurysm. Hypertension especially when not appropriately controlled by medication is another risk factor of this life-threatening event. Combination of increased prevalence of hypertension, aortic dilatation and aneurysms in patients with ADPKD make this complication a significant concern for both patients and clinicians. Taiwanese researchers carried out a large nationwide population-based cohort study on the subject. They utilized the data from Taiwan National Health Insurance Research Database (NHIRD) gathered between 1997 and 2008. The frequency of aortic dissection in ADPKD patients was significantly higher than in the general population (0.92% v.s. 0.11%, $p<0.0001$). Of those, 58% were acute aortic dissection. In addition, Kaplan-Meier curve analysis demonstrated that cumulative incidence of aortic dissection was remarkably higher in the ADPKD than the non-ADPKD group ($p<0.001$) (Sung et al., 2017).

Abnormalities regarding the mitral valve constitute the majority of valvular disease in ADPKD patients. Mitral valve prolapse is particularly common in earlier stages of the disease. It is believed to be caused by underlying gene mutations. As the disease progresses the mitral valve's function becomes even more altered leading to mitral regurgitation. In the later stages of the disease additional valvular abnormalities include degenerative mitral and aortic valve disease, exacerbated by the progression of chronic kidney disease (Morningstar et al., 2021). The pathomechanisms resulting in valvular abnormalities can also be connected with altered function of the PC-1 and PC-2 proteins. Histological examinations of mitral and aortic valve tissue in patients with ADPKD found myxomatous degeneration which is characterized by the loss and disruption of collagen (Lumiaho et al., 2021). Those changes in collagen pose a potential cause for the malfunction of valves inside the heart.

Left ventricular hypertrophy (LVH) and remodelling of the cardiac tissues is another extrarenal representation of ADPKD. There are an array of factors contributing to the development of this complication, among them the extrarenal representations discussed

previously such as hypertension and valvular disease. LVH can be characterized by myocyte hypertrophy and perivascular and interstitial fibrosis (Ebrahimi et al., 2025). Reports of the prevalence of LVH among patients with ADKPD differ. It has been suggested to affect up to 66% of patients (Kuo et al., 2023).

The main mechanism leading to LVH is believed to be secondary to hypertension. However new evidence emerges suggesting other cardiac remodelling processes. The PC-1 protein is expressed on cardiomyocytes and its function is to stabilize and degrade L-type calcium channels. In ADPKD mutations of PC-1 cause a reduction in the α1C subunit of the L-type calcium channel which in turn contributes to the progression of ventricular hypertrophy and fibrosis (Marquez-Nogueras et al., 2023). The PC-2 protein also plays a role as the alteration in its function causes a reduced cardiac shortening and cardiac desynchrony. (Sagar et al., 2023).

Intracranial aneurysms:

Among the most significant of extrarenal complications of patients diagnosed with ADPKD is the development of intracranial aneurysms (ICAs). Rupture of an ICA is considered the most devastating complication of ADPKD (Sanchis et al., 2019).

The prevalence of unruptured ICAs in the general adult population is estimated to be around 3% (Walker et al., 2023). In contrast, the prevalence in adults with ADPKD is significantly higher, reported to be between 9% and 12% (Flahault et al., 2016). A large systematic review and meta-analysis calculated that ADPKD patients have a 6.9-fold higher prevalence of ICAs compared to the general population (Vlak et al., 2011).

Despite this high prevalence, rupture events remain rare (Flahault et al., 2016). The overall rupture rate in large ADPKD cohorts is estimated to be approximately 0.04 per 100 patient-years. However, this rate is still about five times higher than that of the general population (Sanchis et al., 2019). Furthermore, when ruptures do occur in ADPKD patients, they tend to happen at a younger age: a mean age of 41 years, versus 51 years in the general population (Flahault et al., 2016).

ICAs are not considered congenital; rather, they are acquired vascular lesions that develop over a patient's lifetime (Izumo et al., 2022; Etminan et al., 2016). The underlying mechanism in ADPKD ICA formation is linked to its genetic cause as in other extrarenal manifestations. The majority of ICA cases are caused by mutations in the *PKD1* gene (approx. 85% of cases) or the *PKD2* gene (approx. 15%).

Most aneurysms detected by presymptomatic screening in ADPKD patients are small (median diameter of 4 mm). The risk of rupture increases significantly in aneurysms larger than 7-10 mm. The majority of ICAs (85-90%) in ADPKD patients are located in the anterior circulation. This is a favorable finding, as aneurysms in the posterior circulation are associated with a higher risk of rupture (Etminan et al., 2016).

Several factors have been identified that increase the risk of either developing an ICA or of an existing one rupturing in the ADPKD population. A positive family history of ICAs or subarachnoid hemorrhage (SAH) is the most significant risk factor. In one large study, the prevalence of ICAs in ADPKD patients with a family history of SAH was 22%, compared to just 7% in those without such a history (Sanchis et al., 2019). A meta-analysis found a 3.4-fold increased prevalence ratio for those with a positive family history (Vlak et al., 2011). Hypertension and smoking are consistently identified as major modifiable risk factors for both ICA development and rupture. Also being female is recognized as a non-modifiable risk factor for aneurysm development in the general population.

Whether to screen ADPKD patients for unruptured ICAs is one of the most controversial topics in the management of the disease. Current recommendations are largely based on expert opinion and studies with low levels of evidence. Practices vary widely among physicians.

The two main approaches include systematic screening and targeted screening. In the first one screening includes all patients with ADPKD. Proponents argue that it is cost-effective and provides the highest gain in quality-adjusted life years (QALYs). In the second one screening is reserved for individuals with specific high-risk profiles. This is the more widely accepted approach. Major guidelines, including the KDIGO consensus, do not recommend systematic screening for all patients (Sanchis et al., 2019; Walker et al., 2023).

The screening method of choice is a non-contrast, time-of-flight magnetic resonance angiography (TOF-MRA) (Flahault et al., 2016). This modality avoids the need for potentially nephrotoxic gadolinium contrast. However, a 2016 survey revealed a significant knowledge gap, with 73% of responding nephrologists incorrectly believing that contrast was necessary to screen for ICAs. If an initial screening is negative, de novo aneurysms can still form later in life. Therefore, for high-risk patients, rescreening at 5- to 10-year intervals is often recommended.

Conclusions:

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is recognized as the most prevalent hereditary kidney disease, affecting an estimated 10 million people worldwide. The condition is caused by mutations in the PKD1 and PKD2 genes. Its manifestations extend far beyond the kidneys. The polycystin proteins PC-1 and PC-2 are widely expressed in tissues ranging from the liver to the heart and cerebral vasculature, confirming that ADPKD is a multisystem disorder with crucial extrarenal implications that demand a comprehensive, multi-disciplinary approach to patient management.

The comprehensive literature review highlighted three principal extrarenal domains of concern. Firstly, Autosomal Dominant Polycystic Liver Disease ADPLD - most common manifestation, occurring in up to 94% of affected individuals by middle age. It is important to note that, ADPLD is significantly more severe and prevalent in women than men. This difference is strongly attributed to estrogen exposure (e.g., oral contraceptives, multiple pregnancies). While gene mutations pose a primary cause, these additional factors accelerate the progress of ADPLD, necessitating careful hormonal counseling for female patients.

Secondly, ADPKD profoundly impacts the cardiovascular system, effectively acting as a vasculopathy. This effect is primarily mediated by early and refractory hypertension. This effect can be attributed to both renal ischemia-induced RAAS activation and impaired vascular endothelial function. These factors contribute to a heightened risk of complications, including Left Ventricular Hypertrophy LVH, valvular disease (most commonly mitral prolapse), aortic dilatation and aneurysms. Studies confirm that ADPKD patients have significantly wider aortic root diameters and a remarkably increased frequency of aortic dissection compared to the general population.

Finally, the most devastating extrarenal complication is the development of Intracranial Aneurysms ICAs. The prevalence of ICAs in ADPKD patients is approximately seven times higher than in the general population, although rupture events remain rare. When rupture does occur, it is often at a younger age. The most significant risk factor is a positive family history of ICAs or subarachnoid hemorrhage (SAH), followed by uncontrolled hypertension.

The data analyzed confirm that the risk profile for an ADPKD patient extends far beyond the risk of end-stage renal disease (ESRD). Effective patient care must therefore be holistic and proactive. Aggressive blood pressure control is the single most important modifiable

intervention, impacting the progression of LVH, mitigating aortic dissection risk, and reducing ICA rupture risk. Regular cardiovascular surveillance, including echocardiography, should be integrated into routine follow-up. Systematic screening for ICAs in all patients is not currently recommended by major guidelines. Instead, targeted screening using non-contrast Time-of-Flight Magnetic Resonance Angiography (TOF-MRA) should be reserved for high-risk individuals, specifically those with a known family history of rupture or aneurysm.

Further research is needed to fully describe the extrarenal pathogenic role of PC-1 and PC-2 proteins outside of the kidney, independent of uremia and hypertension. Understanding these mechanisms could pave the way for novel, targeted therapies that specifically mitigate the systemic vascular and proliferative risks of ADPKD. Clinical focus should remain on early diagnosis, risk stratification, and rigorous management of hypertension and hormonal factors to improve the long-term prognosis and quality of life for this patient group.

Disclosure

Author's contributions

Conceptualization:ES;
Methodology:VP, ES;
Software:ES;Check:VP;
Formal analysis:ES
Investigation:ES,VP
Resources:ES,VP
Data curation:ES,VP;
Writing-rough preparation:VP
Writing-review and editing:ES,VP
Supervision:ES

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