

Intracranial Aneurysms In Autosomal Dominant Polycystic Kidney Disease: A Nephrologist's Perspective

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) belongs to the most common genetic disorders, and affects approximately 1 in 1,000 people in the general population. It is well-known risk factor for intracranial aneurysms (IAs). However, universal screening for IAs in ADPKD patients remains controversial. Nevertheless, to improve patients' outcomes, patients at risk for IAs should be identified, screened, and prophylactically treated if required. From the point of view of a nephrologist, it is crucial to answer two questions: (1) which ADPKD patients should undergo screening for IAs; and (2) how this screening should be done. These issues are discussed in the paper.

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Key words: Autosomal dominant polycystic kidney disease; Intracranial aneurysms; Magnetic resonance angiography; Screening

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Abbreviations

ABPM: ambulatory blood pressure monitoring;

ADPKD: autosomal dominant polycystic kidney disease;

AH: arterial hypertension;

CTA: computed tomography angiography;

ESRD: end-stage renal disease;

IA: intracranial aneurysm;

MR: magnetic resonance;

MRA: magnetic resonance angiography

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) belongs to the most common genetic disorders, and affects approximately 1 in 1,000 people in the general population. The disease is due to the mutation in one of two genes: PKD1 in type 1, or PKD2 in type 2 of ADPKD. Mutation of PKD1 is more prevalent and causes 85% of cases of the disease. In a large proportion of patients, ADPKD leads to end-stage renal disease (ESRD)^[1]. The average age of ESRD depends on the type of the disease and amounts to 58.1 years in type 1, and 79.7 years in type 2^[2]. Due to the extrarenal distribution of polycystins, encoded by PKD1 and PKD2 genes, ADPKD is a systemic disease, with multiple extrarenal manifestations, including arterial hypertension, aneurysms, and cysts in solid organs, like liver, pancreas, and spleen^[1].

ADPKD is well-known risk factor for intracranial aneurysms (IAs)^[3]. The frequency of IAs in ADPKD is increased compared to the general population, and estimated to 4-22.5%^[4,5]. Aneurysm formation is due to the ciliopathy-related dysfunction of the vascular wall in a mechanism dependent on downregulation of survivin expression^[6]. The rupture of an IA is associated with a high risk of serious complications or death^[7,8]. The age of IA rupture is lower in ADPKD compared to the general population. Additionally, ADPKD is connected to increased morbidity and mortality due to the rupture of IA^[9].

Despite these facts, universal screening for IAs in ADPKD population remains controversial, mainly due to the potential risk connected to pre-emptive treatment of IA, and costs associated with screening^[10]. However, to improve patients' outcomes, patients at risk for IA should be identified, screened, and prophylactically treated if required. From the point of view of a nephrologist, it is crucial to answer two questions: (1) which ADPKD patients should undergo screening for IAs; and (2) how this screening should be done. The aim of the article is to review the indications for screening as well as the methods of it based on current literature on the subject.

INDICATIONS FOR SCREENING FOR INTRACRANIAL ANEURYSMS

Family history of intracranial aneurysm

IAs occur more frequently in ADPKD patients with a family history for IA compared to those without a family history^[11,12,13]. Therefore, family history of IA is the main indisputable indication for screening for IA. In general, all involved members of a family have the same type of mutation, what suggest that the type of mutation correlates with a risk for IA. Then, an ADPKD patient with a history of IA in a family member requires screening regardless of the degree of kinship.

It was not specified at which age the screening should be started in this group. However, rupture of IA in ADPKD may occur even at a very young age^[14,15]. Thus, it is rather not judicious to define a threshold age, below which the screening is not recommended.

Also, a patient with a past history of IA requires periodic follow-up for new IAs.

Neurological symptoms

Symptoms suggestive of IA are considered an indication for IA screening in ADPKD^[16]. However, which symptoms should be considered as suggestive of IA, remains controversial. While focal neurological deficits are obvious indications for neurological assessment including the possibility of IA, headache was questioned to be a symptom of IA^[17]. Headache is observed in 15-49% of ADPKD patients^[17,18], and may be caused by other reasons, for example arterial hypertension, which is common in ADPKD; up to 60% of young ADPKD patients with normal renal function are hypertensive^[19], and the overall prevalence of hypertension exceeds 80%^[20]. On the other hand, in the general population, headache may be a manifestation of IA; according to Lebedeva *et al*^[21], IAs are connected to increased frequency of migraine, and the remission of migraine was observed after clipping of IA^[22]. In my opinion, there is no reason to think it is not a case in ADPKD patients. Indeed, according to our small, retrospective analysis including ADPKD patients who passed a non-fatal rupture of IA, half of them complained of headache in months preceding the rupture^[23]. Therefore, I believe that in ADPKD patients reporting headache persisting after normalization of blood pressure, screening for IA is judicious. Some other authors share my point of view^[24].

Risk of sudden loss of consciousness

According to guidelines^[16], ADPKD patients with job or hobby in which loss of consciousness may be lethal, should undergo screening for IA. Obvious examples of such cases include airplane pilots, bus drivers, paratroopers, and others. However, this indication leaves the field open to interpretation, and eventually, this group may become very wide, as each person with driving license meets this criterion.

Major elective surgery

Due to the risk of IA rupture during surgery, screening is recommended as a part of preparation for a major elective surgery^[16]. However, it has not been specified which procedures should be considered as "major," and whether native nephrectomy, or renal transplantation belongs to this category. It is important, as a large group of ADPKD patients after 50th year-of-age develops ESRD, and they become candidates for renal transplantation as a treatment of choice^[25]. Additionally, 20% of them require native nephrectomy before, or simultaneously with transplant procedure^[26]. Moreover, ADPKD patients with ESRD have increased risk for a hemorrhagic stroke compared to other ESRD reasons^[27]. Although screening for IA is not always considered a routine procedure before native nephrectomy, or renal transplantation, it is increasingly performed in such cases. In some centers, as much as 90% of ADPKD patients who underwent renal transplantation, had the screening performed^[28].

Extreme anxiety of the patient regarding the risk of IA

When an ADPKD patient is extremely anxious of having IA, the screening for it should be done^[16]. The anxiety may be connected to, or heightened by, the patients' knowledge from non-medical sources, like for example websites. However, it is difficult to clearly differentiate between extreme and mild or moderate anxiety. Therefore, I feel it is reasonable to screen each patient who expresses his, or her, anxiety.

Age

The occurrence of IAs increases with patients' age. In a Chinese study, the prevalence of IAs in ADPKD increased after 30th year of age, reaching the peak value between 60 and 69 years of age^[12]. The increase in prevalence of IAs was also reported in Caucasian ADPKD patients; however, it started to increase after the age of 45 years^[29]. Taking together the increasing risk for IAs with age, and, mentioned above, the probability of need for surgery in this patients, it should be a subject to discussion whether the patient age should become an indication for screening for IAs in ADPKD.

Hypertension

Arterial hypertension (AH) is a risk factor for IAs in the general population^[30], but is not considered a risk factor for IAs in ADPKD^[10]. In fact, the relative risk for IAs in ADPKD patients is higher compared to patients with primary AH^[31]. It is connected to the fact that IAs in ADPKD are mainly due to the disease-specific dysfunction of the vascular wall^[6], and ADPKD-associated secondary hypertension is of relatively low significance for the development of IAs. Therefore, the diagnosis of AH, which is common in ADPKD^[32], is not helpful in selection of patients requiring screening for IAs. However, the dysfunction of vascular wall belongs to main pathomechanisms of secondary AH in ADPKD^[32]. Most probably that is why there are some links between development of IAs and AH in ADPKD patients. In a study of Xu *et al*^[12], occurrence of IAs was correlated with the duration of AH. However, it is not easy to employ this finding into the clinical practice, as precise estimation of the duration of AH may be difficult due to the fact that AH may be asymptomatic, and its diagnosis is often delayed. Additionally, in our study^[33], development of IAs positively correlated with some blood pressure parameters measured with ambulatory blood pressure monitoring (ABPM). We suggested that these associations may reflect the severity of the ciliopathy-related vascular wall dysfunction, reflecting in both IA development, and the severity of AH. However, further studies are needed to confirm our findings and to determine

levels of blood pressure parameters suggesting of IA development. Afterwards, the ABPM software should be designed to automatic descry of these abnormalities.

Future perspectives

Clustering of IAs in families suggests that the type of mutation correlates with the risk for IA development. According to the literature, IAs occur in both types of the disease, but patients with type 1 are more likely to develop vascular complication when they have a mutation to the 5' half of PKD1^[34]. Therefore, with future progress in mutation screening it may be possible to identify families at risk for IAs development^[35]. Additionally, in families with IAs without ADPKD, a number of genes/proteins that may reflect the risk for IAs development were identified^[34]. Similarly, circulating microRNAs were proposed to be suggestive of IAs in patients without ADPKD^[36]. These potential markers need to be tested in ADPKD patients to assess whether they may be helpful in selection of patients for screening.

METHODS OF SCREENING FOR INTRACRANIAL ANEURYSMS

The method of choice in detecting IAs in ADPKD is the magnetic resonance angiography (MRA) due to the lack of X-ray exposure and no need for contrast media administration^[29]. In patients with contraindications for MRA, including implanted electronic devices, or ferromagnetic foreign bodies as the most important ones, computed tomography angiography (CTA) should be implemented, as an alternative method. However, in such cases, risk for contrast induced-acute kidney injury, especially in patients with impaired renal function, must always be kept in mind, and preventive measures have to be used. Positive results of MRA usually require confirmation with CTA^[29].

FINAL REMARKS

The patient with IA detected on imaging should be referred to a specialist in neurosurgery in order to decide whether the treatment is required, and, if yes, when, and how (endovascularly or surgically) it should be done. Due to the facts that the risk for enlargement and rupture of IA in ADPKD is quite low and is not higher compared to the general population^[13,37], and, on the other hand, the rate of complications of IA treatment, at least endovascular, is increased compared to the general population^[4], the decision on treatment must be deliberate, and only patients with high risk for IA rupture should be treated. If the treatment is not conducted, the method and timing of follow-up need to be determined.

Despite the fact that the risk for development of new IAs is low^[13], I feel it is judicious to repeat the screening periodically, notwithstanding negative result at the previous examination. While I do not propose any specific intervals between MR imaging, I think that quinquennial seems reasonable. Additional issue is that MRA has limited specificity, especially in detecting very small IAs, which not a bene, have minimal risk for rupture. Therefore, suspicion of an IA ≤ 2 mm in diameter should not be verified with CTA, but may only require periodic follow-ups with MRA, and should only be verified in case of enlargement. Again, there is no data to support any specific intervals between successive examinations, but once a year seems reasonable^[29].

Data on benefits of screening for IAs in ADPKD are suboptimal. Almost 2 decades ago, Butler *et al*^[38] presented results of a decision

analysis supporting routine screening with MRA. Seven years later, benefits of screening ADPKD patients without a history of IA rupture were impeached^[39]. There have been no literature data on the risk-benefit analysis of screening for IAs in ADPKD from the last decade.

CONCLUSIONS

It is well known that ADPKD is a risk factor for IAs. Also, effective methods for the diagnosis and treatment of IAs are available. Therefore, in the 21st century, it is hardly acceptable that there are still patients who die or become disabled due to the rupture of an IA. Then, attempts to develop a set of criteria for screening for IAs are worth of recognition. However, current criteria are of suboptimal precision, and leave the field open to interpretation. They need polishing, as according to some of them, the vast majority of ADPKD patients should be screened, what I do not expect to be widely acceptable. Additionally, in my opinion, what is also important in prevention of IA rupture in ADPKD, is the awareness of patients and their physicians, of the risk. Therefore, in addition to the efforts for optimization of screening indications, education of both patients, and physicians, is necessary.

CONFLICT OF INTERESTS

The author declare no conflict of interest.

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