

Intracranial Manifestations of Autosomal Dominant Polycystic Kidney Disease

Andrzej Kulesza, Monika Gradzik, Mariusz Niemczyk

Andrzej Kulesza, Mariusz Niemczyk, Department of Immunology, Transplant Medicine and Internal Diseases; Medical University of Warsaw; Warsaw, Poland

Monika Gradzik, Department of Radiology; Medical University of Warsaw; Warsaw, Poland

Correspondence to: Mariusz Niemczyk, Department of Immunology, Transplant Medicine and Internal Diseases; Medical University of Warsaw; Nowogrodzka 59, 02-005 Warsaw, Poland.

Email: mariusznieńczyk@wp.pl

Telephone: +48-22-5021641

Fax: +48-22-5022127

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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. ADPKD is a systemic disease, with multiple extrarenal manifestations, like arterial hypertension, aneurysms, and cysts in solid organs, including liver, pancreas, and spleen. Among intracranial manifestations of ADPKD, the most important are intracranial aneurysms. ADPKD is a well-known risk factor for them. Additionally, arachnoid cysts may be found in some ADPKD patients. Rarely, pineal cysts and choroid plexus cysts are observed in this population. The aim of our paper is to present intracranial manifestations that may be observed in ADPKD.

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Key words: Autosomal dominant polycystic kidney disease; Arachnoid cyst; Intracranial aneurysm; Magnetic resonance angiography; Screening; Treatment

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Abbreviations

ADPKD: Autosomal dominant polycystic kidney disease;

CTA: computed tomography angiography;

ESRD: end-stage renal disease;

IA: intracranial aneurysm;

MRA: magnetic resonance angiography;

SAH: subarachnoid hemorrhage.

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 caused by a mutation in one of two genes: PKD1 or PKD2 in type 1 or type 2 of ADPKD, respectively. Mutation of PKD1 is more common 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 years in type 1, and 80 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].

Among intracranial manifestations of ADPKD, the most important are intracranial aneurysms (IAs). ADPKD is a well-known risk factor for them^[3]. Additionally, arachnoid cysts may be found in some ADPKD patients. Rarely, pineal cysts and choroid plexus cysts are observed in this population^[4]. The aim of our paper is to present the topic of intracranial manifestations that may be observed in ADPKD.

INTRACRANIAL ANEURYSMS

Amongst extrarenal manifestations of ADPKD, intracranial aneurysms (IAs) attract most attention due to serious complications associated with aneurysm rupture - disability, cognitive impairment, and in many cases death^[5,6]. In the general population IAs occur in approximately 3% of people^[7], and their frequency increases

with age^[8,9]. IAs account for 80% of non-traumatic subarachnoid hemorrhages (SAHs)^[10]. ADPKD is the most common heritable condition associated with aneurysm formation. IAs are more likely to occur in ADPKD patients than in the general population with higher rupture incidence^[1,3,11,12], and are responsible for a large proportion of deaths in this group of patients^[11-13]. IAs occur in 4-22,5% of patients with ADPKD^[12,14,15], which is 4 - 5 times more often than in the general population^[13,16] and their incidence in this group increases with age, reaching over 22% after the age of 45 years^[17]. In a prospective screening study conducted by Pirson *et al.*, IAs appeared in 16% of ADPKD patients with positive family history and in 6% with negative IAs family history^[6]. In a study conducted by Niemczyk *et al.*, IAs were detected in 16.9% patients with ADPKD, and 6% of this group required surgery^[17]. Although most of the detected asymptomatic IAs in ADPKD patients are relatively small, incidence of IAs with a diameter greater than 10mm is much higher in comparison with the general population (27% vs 7%)^[13,18]. Asymptomatic aneurysms are usually small with a meager risk of rupture^[17,19], although 50% of aneurysms leading to SAH are smaller than 10 mm^[10,24].

In ADPKD aneurysms are caused by alterations in the vasculature directly linked to PKD1 or PKD2 mutation^[20]. Studies suggested direct involvement of PKD1 and PKD2 in the pathogenesis of IAs, and a similar pathogenetic pattern can be seen in aortic dissection or dolichoectatic intracranial arteries^[21]. Polycystins are localized in specialized structures responsible for perception of extracellular stimuli (primary cilia, focal adhesions and adherent complexes) and play an important role in calcium homeostasis. Altered calcium cellular distribution may be in relation with IAs pathogenesis in ADPKD^[22]. Recent findings suggest that polycystin gene mutation may lead to down-regulation of survivin – apoptosis inhibitor, and one of the cellular cycle controllers. It has been shown that survivin insufficiency in cells forming aneurysms and renal cysts walls in ADPKD patients leads to DNA accumulation and cell number reduction, which results in tissue malfunction^[23].

Cerebral aneurysms incidence in the general population as well as in ADPKD patients increases with age. In a study conducted by Niemczyk *et al.* only one IA was found in a person younger than 45 years. In the very same study among patients older than 45 years 22.4% had IAs and almost 50% of this group required neurosurgery. Authors suggested that screening should be conducted in patients with ADPKD older than 45 years^[17], though subarachnoid hemorrhage in ADPKD typically appears at younger age, on the average of 40 years^[5,24]. In majority of analyzes there were no differences found between sexes in terms of IAs frequency in ADPKD^[14,15,17,29]. Interestingly in the general population IAs are more frequently diagnosed in woman (woman to man proportion is 3: 1)^[3,25] and are more likely to occur in Afro-Americans^[26]. In the general population most common localization for IAs is the internal carotid artery^[11,13,18], in the ADPKD most aneurysms can be found in the anterior circulation, with the highest prevalence in the middle cerebral artery^[17,19]. Some authors report posterior circulation as a rare localization^[12,18,19].

Modifiable risk factors for aneurysm formation in the general population are active tobacco smoking, arterial hypertension, and heavy alcohol consumption. Estrogen intake might also be a risk factor^[27], and some authors suggest coffee consumption and use of cocaine^[28]. Non-modifiable risk factors are: positive family history for IAs, ADPKD and some rarer inheritable conditions such as type IV Ehlers-Danlos disease^[29], type 1 neurofibromatosis and Marfan's syndrome^[30]. In ADPKD, positive family history is also considered a

risk factor for IAs formation^[18,19,31]. In patients with ADPKD affected with aneurysm 40% have a positive family history compared with 10% in the general population^[32]. The risk of aneurysm formation increases with the number of first degree relatives with aneurysms or those who have had SAH^[13,32]. Although arterial hypertension affects up to 75% of patients with ADPKD and normal renal function^[33], IAs development in ADPKD is unrelated to arterial hypertension, what differentiates them from the general population^[5,18]. It has been shown, however, that although hypertension itself is not a risk factor for IAs formation in the population of patients with ADPKD, aneurysms prevalence correlates with the duration of hypertension. No relationship between IA formation and renal function has been shown^[19].

ADPKD is responsible only for less than 1% of all SAHs due to its relatively rare occurrence in the general population^[18,34]. IA rupture usually occurs in patients with ADPKD at younger age than in the general population, often in patients with preserved renal function^[5]. Morbidity and mortality due to SAH is also greater in ADPKD^[35] with a mortality rate of 46%^[36]. In the population of patients with ADPKD most common location of ruptured aneurysms is anterior circulation^[19], especially the anterior communicating artery^[32]. The highest risk of subarachnoid hemorrhage in the general population is related to positive family history, although the most important population factors are smoking, and hypertension^[11,37]. A positive family history is interpreted as at least one first-degree relative with SAH. In ADPKD, family history is also an important risk factor^[19,31], and it is positive in up to 30% of patients with bleeding^[15]. SAH risk is higher in siblings than in relation children-parents^[13,32,38]. Gieteling *et al.* shown that the mean age of the SAH occurrence in patients with ADPKD is 41 years^[18], which is lower in comparison with the general (57 years)^[18,35]. Also predominance of women in this group is not so clear. Usually, the IA rupture occurs before the age 50 years (64%)^[5,12,13,28].

SCREENING FOR INTRACRANIAL ANEURYSMS

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^[12]. It is worth noting that benefits from the information obtained in the course of screening are often difficult to clearly assess. Most of the detected changes are small and do not qualify for neurosurgical treatment, and in the case of larger changes the risk of complications due to surgery is significant^[39]. Therefore prior to the screening procedure the risk and possible benefits of the test should be considered. Patients anxiety accompanying the examination, and the stress associated with the detection of a small aneurysm not qualifying for surgery, but only to follow-up, should also be taken into consideration. Some authors acknowledge positive family history (in the general population), and ADPKD as the two basic indications to actively search for aneurysms^[11], and recommend screening in all patients with ADPKD^[40]. However, most authors agree that due to small diameter of the majority of aneurysms in ADPKD, their localization mainly in the anterior circulation, and therefore small probability of rupture, screening should be proposed only in chosen groups of ADPKD population^[14]. At present, indications for screening are limited to patients with a history of subarachnoid hemorrhage in whom the risk of new aneurysm formation is 1.8% per year, and the risk of undergoing a new SAH is significantly higher^[41], as well as in patients with a positive family history for SAH, those qualified

for a major surgery, or in occupation or hobby in which loss of consciousness could be dangerous (pilots, etc.), or patients in which there is anxiety associated with risk of SAH^[35,42-45]. It appears that ADPKD patients with a history of SAH are a group which would benefit most from the screening^[14]. Due to the fact that in the group of ADPKD patients older than 45 years over 50% will require surgery due to kidney disease progression, some authors propose screening in all patients with ADPKD who have reached that age^[17]. In the literature there are also proposals for screening in patients who have reached 30 years^[19]. For patients with ADPKD, and a positive family history of SAH it is proposed to start screening before the age of 20 because only 2.5-10% of bleedings in this group are disclosed at such a young age^[6]. Symptoms suggestive of IA are considered an indication for IA screening in ADPKD^[42]. Also, headache is given by some as a potential indication for screening^[24]. However, headache is not a specific symptom, though in the general population unruptured IAs are often associated with the occurrence of migraine without aura^[46]. Characteristic symptom is also pain above and behind the eye^[47]. Because headache is often associated with hypertension particular attention should be paid when it is present after normalization of blood pressure^[24].

In the case of a negative screening outcome in the general population it is recommended to re-examine, because the risk of finding an aneurysm after 5 years after the magnetic resonance angiography (MRA) procedure is 7%^[48]. It is not entirely certain what interval should be recommended in ADPKD. Re-screening in ADPKD patients is controversial because of the low incidence of aneurysms in patients negative at the first test - 2.6%. It appears that re-screening should be considered in case of a positive SAH family history^[49]. In case of detecting a small inoperable aneurysm an interval of 2 - 5 years is recommended, although these suggestions are not supported by evidence^[37]. Niemczyk *et al.* proposed that all patients older than 45 years should undergo MRA, and in case of suspicion of IA larger than 2mm a computed tomography angiography (CTA) revision should be recommended, and if verified - consulted by a neurosurgery specialist. When IA smaller than 2mm is suspected – follow-up should be considered^[17]. As the maximum age for screening some authors give 60-70 years depending on individual health status, due to the short potential survival time^[11].

SCREENING METHODS

Non-invasive imaging techniques such as MRA and CTA are particularly useful in intracranial aneurysms detection. Diagnostic performance of CTA and MRA is similar^[50], and in both cases the tendency to overlook small changes is congruent, although CTA sensitivity for smaller aneurysms is slightly higher. MRA does not involve exposure to harmful radiation and does not require potentially nephrotoxic intravenous contrast administration, what makes it a method of choice in the screening for IAs in ADPKD (Figure 1). It should be noted, however, that sensitivity of this technique is limited in case of small aneurysms^[17]. It has been shown that sensitivity for aneurysms with diameter exceeding 6 mm is as high as 100%, but only 55.6% for aneurysms smaller than 3 mm^[51]. In other studies, the results were even lower with sensitivity of approximately 30% for lesions of less than 5 mm in diameter^[50]. In patients after clipping procedure MRA image is interrupted by significant artifacts, so CTA is preferable in this group^[52]. In the case of intravascular coiling MRA is the preferred technique^[53,54].

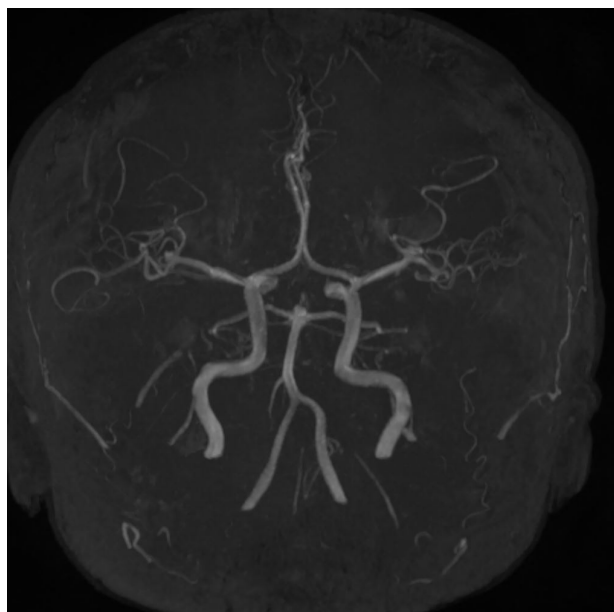


Figure 1 Magnetic resonance angiography. Multiple intracranial aneurysms (final section of basilar artery, and the division of both middle cerebral arteries) in a 37-year-old male with autosomal dominant polycystic kidney disease and arterial hypertension.

TREATMENT OF INTRACRANIAL ANEURYSMS

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^[15,35], and, on the other hand, the rate of complications of IA treatment, at least endovascular, is increased compared to the general population^[8], the decision on treatment must be deliberate, and only patient 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. In all patients with IAs, smoking cessation and control of cardiovascular risk factors are recommended^[55]. In general, indications for treatment are based on those applied in the general population. Large (≥ 12 mm in diameter), symptomatic, or enlarging IAs are indications for treatment. Possibly, treatment should be considered when the IA is 7-12 mm in diameter, and the patient is young, IA is localized at the posterior circulation or at the posterior communicating artery, the daughter sac is observed, or there is a positive family history for SAH. Similarly, treatment should be considered in young patients with smaller (<7 mm in diameter) IA, when 1 of the 3 latter features are present. Treatment is not recommended in patients with IAs <7 mm in diameter, localized in the anterior circulation, without family history for SAH, without daughter sac, and in cases of asymptomatic cavernous internal carotid aneurysms^[42]. Small, untreated IAs require reevaluation every 6-24 months^[55]. It is important that the intervention is personalized^[42]. Depending on the capabilities of the center and specific indications, open surgery (clipping) or endovascular methods (coiling) are used. Coils are the preferred method of treatment aneurysms localized in the posterior circulation and in lesions difficult to access surgically^[56]. Overall risk of death or permanent disability following treatment of ruptured aneurysm is approximately 5%, and for permanent cognitive

functions impairment is about 10%. Some authors believe that risk is higher for neurosurgical clipping than endovascular coiling^[57,58]. The risk associated with surgery is the higher the larger is the IA diameter, so aneurysms detected during screening procedure as generally smaller are associated with slightly lower risk^[59]. Giant and posterior circulation aneurysms have a higher rate of postoperative complications compared with small anterior circulation aneurysms^[60]. In one study, unruptured aneurysm coil embolization was associated with permanent complication rate of 6.7% and 1.4% mortality^[58]. Total occlusion was achieved in only 45% of patients, which is associated with a high prevalence of subsequent recanalization^[61]. Endovascular coiling is also associated with the risk of aneurysm expansion^[62] in 10-15% of patients within 3 years following surgery^[63]. Overall morbidity and mortality in patients who underwent surgical clipping due to asymptomatic aneurysms detection in the course of screening a month after surgery was 17.5% (mortality - 2.3%, significant disability - 9.7%, cognitive impairment - 11.6%). After one year the results were slightly higher. Combined morbidity and mortality was twice as high in patients aged 45 - 64 years, compared with patients younger than 45 years, and nearly five times higher in the group older than 64 years^[39].

Most probably, due to the differences in pathogenesis as well as clinical characteristics of IAs in ADPKD compared to the general population, disease-specific treatment rules should be established in future.

OTHER INTRACRANIAL MANIFESTATIONS OF ADPKD

Other intracranial manifestations of ADPKD are usually incidental findings of low, or no clinical significance. Intracranial arachnoid cysts (Figure 2), an aberration characterized by splitting and duplication of the arachnoid membrane are ten times more common in ADPKD in comparison with the general population^[64]. Their incidence is estimated to 7-8%^[4,65]. In our series of ADPKD patients, their incidence amounted to almost 6%. Arachnoid cysts may be observed both in male and female patients, mainly in posterior, or middle cranial fossa. According to some authors, they may cluster in ADPKD families^[66]. Arachnoid membrane cysts usually do not give any neurological symptoms, and even quite large arachnoid cysts may be asymptomatic^[67]. However, headaches, seizures and focal neurological deficits are possible. Possible complications of arachnoid cysts are chronic subdural hematoma, subdural hygroma, intracystic and epidural hematoma. Typically, subdural hemorrhage occurs in young men with middle cranial fossa cysts. Arachnoid cysts require surgery only in rare symptomatic, or complicated cases^[64,68]. Some other intracranial complications in patients with ADPKD are pineal cysts and choroid plexus cysts^[4,69].

CONCLUSIONS

Among intracranial manifestations of ADPKD, IAs require special clinical attention. Their possibility must be always kept in mind during the management of ADPKD patients. In patients with indications, IAs should be actively sought with imaging techniques. If found, deliberative decisions have to be made whether to treat, or to observe them. Additionally, the efforts for optimization of screening and treatment indications are necessary. Arachnoid cysts, pineal cysts, and choroids plexus cysts are less important from the clinical point of view. However, their possibility and clinical significance should be known by those who care for ADPKD patients, to avoid redundant

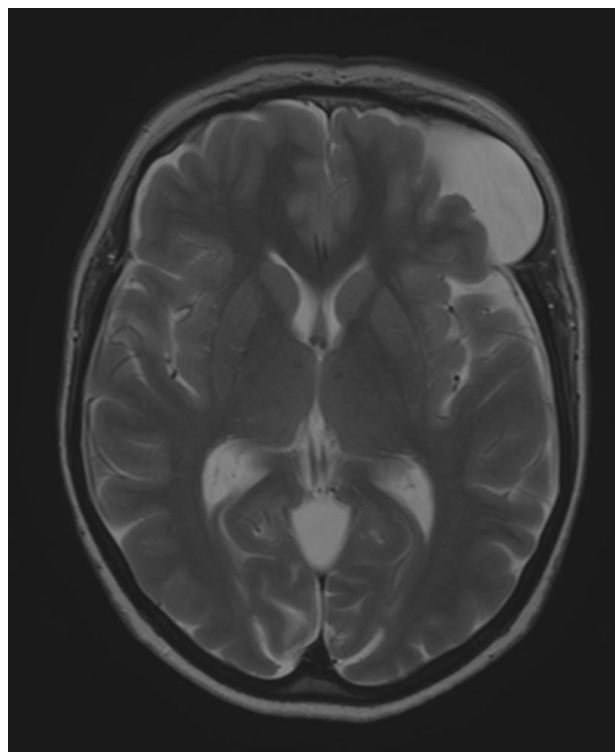


Figure 2 Arachnoid cyst (42x18x37 mm) of the left anterior cranial fossa in a 57-year-old female with autosomal dominant polycystic kidney disease. It was found incidentally during screening for intracranial aneurysms with magnetic resonance angiography. Additionally, little choroid plexus cysts in the trigones of the lateral ventricles were observed in the patient.

investigations and stress when they are incidentally found.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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