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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ANEURYSM

Intracranial aneurysms in patients receiving kidney transplantation for autosomal dominant polycystic kidney disease

Jee Yeon Kim[1] · Seung Chai Jung[2] · Youngmin Ko[1] · Dong Hyun Kim[1] · Ji Yoon Choi[1] · Hyunwook Kwon[1] · Joo Hee Jung[1] · Young Hoon Kim[1] · Duck Jong Han[1] · Sung Shin[1]

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Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, leading to kidney failure. One of the most serious extrarenal complications of ADPKD is comorbid intracranial aneurysms. The aim of this study is to evaluate the prevalence, rupture rate, and treatment outcomes of intracranial aneurysms in ADPKD.

Methods Adult patients with a documented diagnosis of ADPKD who received kidney transplantation at our center from January 1994 to December 2018 were included in the study. Medical history, physical examination, laboratory findings, imaging studies, and operation records were collected and analyzed from our database.

Results Among 154 kidney transplant recipients with ADPKD, 113 (73.4%) patients were screened for intracranial aneurysms preoperatively. Twenty three patients (14.9%) had intracranial aneurysms with mean diameter size of 4.5 ± 2.7 mm. Nine patients (5.8%) experienced aneurysm rupture and the mean age at time of rupture was 34.9 ± 9.3 years. Twelve patients (52.2%) presented with multiple aneurysms. The most common aneurysm location was the bifurcation of the middle cerebral artery (34.9%). Clipping was the most common treatment in both ruptured and unruptured aneurysms.

Conclusions Intracranial aneurysms are more frequent in patients with ADPKD, and the average age of intracranial artery rupture in patients with ADPKD is earlier than in the general population. It is necessary to consider proper evaluation and management of intracranial aneurysms when counseling ADPKD patients who will undergo kidney transplantation.

Keywords Intracranial aneurysm · Polycystic kidney disease · Kidney transplantation · Preoperative evaluation

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, affecting 1 in 400 to 1 in 1000 individuals [13]. Expansion of multiple cysts scattered throughout the renal parenchyma is a characteristic of ADPKD. Cyst expansion produces a dramatic increase in total kidney volume and commonly leads to the development of kidney failure requiring renal replacement therapy and eventually kidney transplantation [22]. In 2011, ADPKD accounted for 8% of incident and 4.8% of prevalent patients on dialysis in the USA [6]. ADPKD is the cause of end-stage renal disease in 2.8% of recipients receiving kidney transplant at our center.

ADPKD has well-documented associations with cardiovascular complications and vascular abnormalities [7, 28]. One of the most serious extrarenal complications of ADPKD is comorbid intracranial aneurysms. The prevalence of aneurysms associated with ADPKD ranges from 4 to 40% [19, 27]. Since few studies have focused on intracranial aneurysms in ADPKD, the natural history and appropriate management strategies for aneurysms in these patients are not completely understood. Evaluating the prevalence, rupture rate, and prognosis of aneurysms in ADPKD patients is important for the management and surveillance of these patients.

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✉ Sung Shin
sshin@amc.seoul.kr

[1] Division of Kidney and Pancreas Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 05505, Republic of Korea

[2] Department of Radiology and Research, Institute of Radiology, University of Ulsan College of Medicine, Seoul, Republic of Korea

We examined the association between ADPKD and intracranial aneurysms by investigating 154 patients who underwent kidney transplantation for ADPKD at our institution. The aim of this study was to report prevalence and distribution of aneurysms in patients with ADPKD. We also assessed the incidence of aneurysm rupture and evaluated outcomes according to treatment modalities.

Material and methods

Participants and data collection

A total of 154 patients with a documented diagnosis of ADPKD underwent kidney transplantation at our center between January 1994 and December 2018. The diagnosis of ADPKD was based on preoperative examinations including ultrasonography or computed tomography (CT) images and post-nephrectomy histologic reports consistent with ADPKD.

Medical history, physical examination, laboratory findings, imaging studies, and operation records were collected from our database. To evaluate intracranial aneurysm characteristics, CT, magnetic resonance (MR), or conventional angiography images were also reviewed. This study received approval from the institutional review board of our center (approval number: 2019-0310).

Screening for aneurysms

Of the 154 ADPKD patients, 113 patients underwent intracranial imaging studies before kidney transplantation, either to verify neurological symptoms or to screen preoperative intracranial lesion. Since 2016, it has been routine to perform intracranial imaging studies for aneurysm screening during the work-up process before kidney transplantation for ADPKD patients at our center.

With this information, we investigated (1) number, location, and size of aneurysms; (2) rupture status of the aneurysms; (3) treatment modality; and (4) complications and radiological outcomes during follow-up.

Nephrectomy and kidney transplantation for ADPKD

In the early era at our center, nephrectomy was performed ahead of kidney transplantation at the surgeon's or nephrologist's discretion. Unilateral or bilateral nephrectomies were indicated when patients presented with signs or symptoms such as pain, hemorrhage or infection of cysts, distention, or dyspepsia or when there was not enough space for kidney allograft due to the large size of polycystic kidneys.

Currently, we routinely perform bilateral nephrectomy and kidney transplantation simultaneously using a long midline incision for ADPKD patients receiving kidney transplantation.

Statistical analysis

Statistical analyses were performed with SPSS 21.0 for Windows (IBM Inc., Armonk, NY). Categorical variables were compared using the chi-square test or Fisher's exact test. All continuous variables were analyzed using the Mann-Whitney test or *t* test depending on the data. A p value of less than 0.05 was considered statistically significant.

Results

Patient characteristics and patients with intracranial aneurysms

Demographic data of the ADPKD patients are summarized in Table 1. Among the 113 patients with preoperative intracranial imaging studies, 23 patients (20.4%) had intracranial aneurysms identified during preoperative imaging studies. Overall, 115 ADPKD patients (74.7%) were diagnosed with hypertension, and there was no significant difference in the hypertension prevalence between the aneurysm and no aneurysm groups ($p = 0.14$). Thirty-eight patients (24.7%) received preemptive kidney transplantation, and the mean time from dialysis to transplant in patients receiving renal replacement therapies was 48.7 months [0.5–192.0]. A total of 30 patients (19.5%) received kidney transplants from deceased donors. There were 2 cases of re-transplantation.

A history of ruptured aneurysm was identified in 9 patients (8.0%) among 113 patients with preoperative imaging, and the mean age of rupture was 34.9 ± 9.3 years. The mean age was significantly higher in those with unruptured aneurysms compared to those with ruptured aneurysm (52.3 ± 5.7 vs. 34.9 ± 9.3 years, $p < 0.001$).

Characteristics of the aneurysms, locations and rupture

Table 2 summarizes the characteristics and location of the aneurysms. Twelve patients (52.2%) presented with multiple aneurysms and the mean number of aneurysm per patient was 1.87. The mean diameter size of unruptured aneurysms was 4.0 ± 2.0 mm [1.8–9.0 mm]. Nearly half of aneurysms were located in the middle cerebral artery (MCA) territory, and the most common location of aneurysm was the MCA bifurcation (34.9%) followed by the anterior communicating artery (AcomA) (20.9%). The nine ruptured aneurysms were found in following locations: three were located at the MCA bifurcation, three at AcomA, two at anterior cerebral artery

Table 1 Recipient and donor characteristics of the ADPKD patients and demographic data of patients with or without aneurysms

	All ($N = 154$)	No aneurysm ($N = 131$)	Aneurysm ($N = 23$)	p value
Age, years (SD)	51.2 ± 8.5	52.4 ± 6.3	51.0 ± 8.8	0.36
Female, *n* (%)	55 (35.7)	47 (35.9)	8 (34.8)	0.92
BMI, kg/m^2 (SD)	23.2 ± 3.1	22.3 ± 2.3	23.4 ± 3.2	0.05
Hypertension, *n* (SD)	115 (74.7)	95 (72.5)	20 (87.0)	0.14
Type of dialysis, *n* (SD)				0.69
HD	108 (70.1)	92 (70.3)	16 (69.6)	
PD	8 (5.2)	5 (3.8)	3 (13.0)	
Preemptive	38 (24.7)	34 (26.0)	4 (17.4)	
Time from dialysis to transplant, month (SD) [range]	48.7 ± 48.9 [0.5–192.0]	32.8 ± 32.8 [0.5–192.0]	51.8 ± 51.1 [2.0–109.0]	0.13
Female donor, *n* (%)	79 (52.7)	65 (51.2)	14 (60.9)	0.39
Donor type, *n* (%)				0.17
Living related	52 (33.8)	46 (35.1)	6 (26.1)	
Living unrelated	72 (46.7)	54 (44.3)	14 (60.9)	
Deceased donor	30 (19.5)	27 (20.6)	3 (13.0)	
Patients with preoperative imaging studies	113 (73.4)			
Patients with unruptured IA			14 (9.1)	
Mean age, years (SD)			52.3 ± 5.7	
Patients with ruptured IA			9 (5.8)	
Mean age, years (SD)			34.9 ± 9.3	

ADPKD, autosomal dominant polycystic kidney disease; *SD*, standard deviation; *BMI*, body mass index; *HD*, hemodialysis; *PD*, peritoneal dialysis; *IA*, intracranial aneurysms

(ACA) territories, and one at vertebral artery. All of these aneurysms were saccular in shape.

Diagnostic and treatment modalities

The most common diagnostic modalities were MR angiography (47.8%) and CT angiography (34.8%) (Table 3). Four-vessel angiography was performed as a diagnostic modality in four patients who initially presented with hemorrhage from ruptured aneurysms. In our study, surgical clipping was the most common treatment in both ruptured and unruptured aneurysms (88.9% and 26.5%) followed by the endovascular approach (11.1% and 20.6%). There were no cerebrovascular accidents during the perioperative admission period in all participants. The mean follow-up duration was 46.5 ± 36.2 months [2.0–121.0] in 23 patients with aneurysms. Among the 25 treated aneurysms, 4 cases (16.0%) showed aneurysm growth or recurrence. There was no re-rupture after treatments (Fig. 1).

Discussion

Intracranial aneurysms are known to be the most common vascular manifestation in patients with ADPKD. Here we investigated 154 patients who underwent kidney transplantation to treat ADPKD. Of the 113ADPKD recipients with preoperative intracranial imagings, 23 patients (20.4%) had aneurysms on their preoperative imaging studies. The most common diagnostic modality was MR angiography. Nearly half of the patients with aneurysms had multiple aneurysms and 20.9% showed history of ruptured aneurysms. The mean diameter size of aneurysms was 4.5 mm. The most common location of aneurysms was the MCA bifurcation (34.9%) and the next most common location was AcomA (20.9%). Accordingly, ruptured aneurysms were most frequently found in the MCA bifurcation and AcomA. The majority of the ruptured aneurysms were treated surgically with clipping. About 16.0% of patients had their aneurysm grow or recur during the follow-up (Fig. 2).

Intracranial aneurysms occur more frequently in patients with ADPKD (9–12%) [12, 14, 31] than in the general population (2–3%) [29] and are more commonly found in families with *PKD1* or *PKD2* mutations. [14, 25] In the general population, a recent retrospective study including 4934 Korean participants with brain magnetic resonance angiography on health examination reported that 5.2% participants were detected with intracranial aneurysms. In this study, 258 participants had 274 intracranial aneurysms [5]. Another national cohort study using Korean National Health Insurance Service (NHIS) database showed 847 among 132,355 subjects developed diagnosis of intracranial aneurysms during a 9-year follow-up and the incidence of intracranial aneurysm was 49.4/100,000 person-years [15]. Our study demonstrated a

Table 2 Anatomic and morphologic characteristics of aneurysms

	Number (%)
Patients with multiple aneurysms, *n* (%)	12 (52.2)
Mean size, mm (SD) [range]	4.5 ± 2.7 [1.8–12.0]
Mean size of unruptured aneurysms, mm (SD) [range]	4.0 ± 2.0 [1.8–9.0]
Ruptured aneurysms, *n* (%)	9 (20.9)
Direction of aneurysms, *n* (%)	
Right	18 (41.9)
Left	21 (48.8)
Midline	4 (9.3)
Anatomic location of aneurysms, *n* (%)	
MCA	20 (46.5)
M1	5 (11.6)
M2	0
Bifurcation	15 (34.9)
ACA	6 (14.0)
A1	1 (2.3)
A2	3 (7.0)
A3	2 (4.7)
Anterior communicating artery	9 (20.9)
Posterior communicating artery	2 (4.7)
ICA	4 (9.3)
VB complex	2 (4.7)

ICA, internal carotid artery; *AchA* anterior choroidal artery; *VB complex*, vertebrobasilar complex; *BA*, basilar artery; *SCA*, superior cerebral artery; *PCA*, posterior cerebral artery; *PICA*, posterior inferior cerebellar artery, vertebral artery

much higher rate of intracranial aneurysm in the ADPKD patients compared to the general Korean population. The difference in rates of intracranial aneurysm rupture in patients with ADPKD and the general population is consistent with the difference in prevalence, suggesting a similar rupture risk in these patients [22]. From previous reports, the average age of patients with ADPKD who experience aneurysm rupture is 41 years, approximately 10 years earlier than in the general population [4, 26], but our study found that the average age of aneurysm rupture tended to be younger at 34.9 years.

Table 3 Aneurysm diagnosis, treatment, and surveillance

	Number (%)
Diagnostic modality (*n* = 23)	
Four-vessel angiography	4 (17.4)
CT angiography	8 (34.8)
MRA	11 (47.8)
Treatment modality (*n* = 43)	
Treatment of ruptured IA (*n* = 9)	
Clipping	8 (88.9)
Coiling or embolization	1 (11.1)
Treatment of unruptured IA (*n* = 34)	
Clipping	9 (26.5)
Coiling or embolization	7 (20.6)
Untreated	18 (52.9)
Recurrence or growth after treatment (*n* = 25)	4 (16.0)

CT, computed tomography; *MRA*, magnetic resonance angiography; *IA*, intracranial aneurysm

A systematic literature review of nine studies found that in ADPKD population, the prevalence of unruptured intracranial aneurysms was 11.5% whereas 1.9% of aneurysms were ruptured, and the mean age of patients with unruptured aneurysms was higher compared to the ruptured population (47.8 vs. 42.5 years). [3] Our study showed a larger difference between the age of ADPKD patients with ruptured and unruptured aneurysms. Also, this systematic review revealed that MCA was the most common location accounting for 35% of all ruptured and unruptured aneurysms, followed by the ACA-AComA (23.5%) [3] which is consistent with our findings.

There is a clear relationship between ADPKD and vascular anomalies. ADPKD is caused by mutations in either one of the two principal genes, *PKD1* located on chromosome 16p13.3 [11] and *PKD2* located on 4q21 [17], coding proteins polycystin-1 and polycystin-2, respectively. The pathogenesis of vascular abnormalities in ADPKD has not been studied as extensively as the mechanisms involved in cyst epithelial cell proliferation and fluid secretion. Several groups have shown

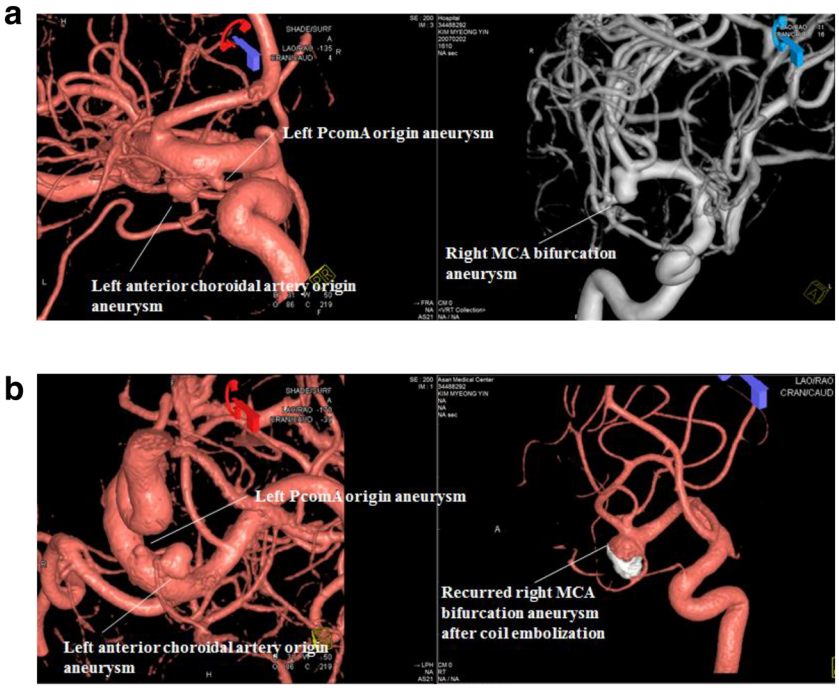

Fig. 1 A 45-year-old male patient with a history of clipping for a left middle cerebral artery (MCA) bifurcation aneurysm rupture at age 26 showed multiple intracranial aneurysms on preoperative images in 2007. (**a**) Initial 4-vessel angiography digital subtraction angiography images identified an 8.3 mm aneurysm at the right MCA bifurcation, and small aneurysms at the left anterior choroidal artery (AChA) and posterior communicating artery (PcomA). Coiling embolization was performed for the right MCA bifurcation aneurysm prior to kidney transplantation. **b** Follow-up 4-vessel angiography digital subtraction angiography in 2012 showed recurrence of the embolized right MCA bifurcation aneurysm and enlargement of the left AChA aneurysm to 4.3 mm. No change in size was observed of in the left PcomA aneurysm

that endothelial dysfunction occurs early in ADPKD, preceding the onset of hypertension. Wang et al. found that relaxation of subcutaneous arteries was significantly impaired in ADPKD patients and suggested that this was due to impaired vascular nitric oxide synthase activity [30]. Hypertension was found in 74.7% of our patients, and a previous systematic

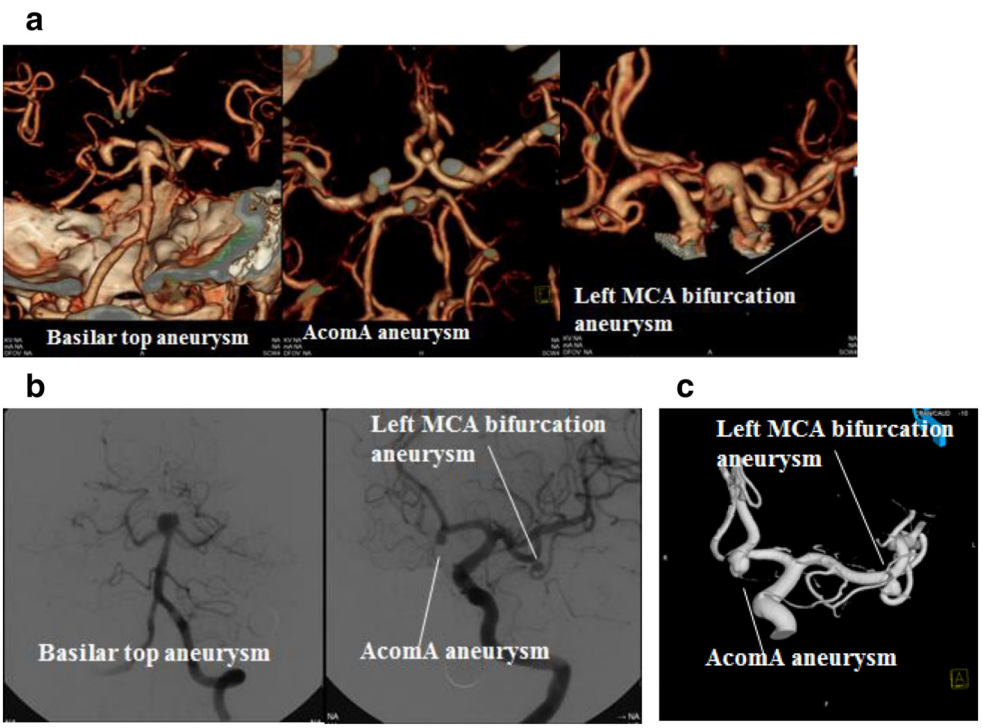

Fig. 2 A 47-year-old female patient presented initially with multiple intracranial aneurysms in 2005. **a** Computed tomography angiography images showed a 7-mm basilar tip aneurysm, and a 3-mm left anterior communicating artery (AcomA), and 3-mm left middle cerebral artery (MCA) bifurcation aneurysms. **b** Magnetic resonance digital subtraction angiography images of the basilar tip, left AcomA, and left MCA bifurcation aneurysms were taken in the same time period. Coiling embolization was performed for the basilar artery aneurysm. **c** Follow-up 4-vessel 3D rotational angiography was performed in 2008. Minimal growth of the left AcomA (3 to 4.7 mm) and no change in the left MCA bifurcation aneurysm was observed. Neither aneurysm was treated. The patient received kidney transplantation in 2012

review also reported a similar rate of hypertension (79.3%) in ADPKD patients [3]. According to a rat model study of ADPKD, increased endothelin-1 generation by the cysts may also contribute to endothelial dysfunction and hypertension [10]. Kocaman et al. assessed endothelial function in vivo by flow-mediated dilation of brachial arteries and demonstrated severe impairment of both endothelium-dependent and independent vasodilation in ADPKD patients. In addition, this study showed structural changes by finding increased carotid intima-media thickness in ADPKD group [16].

Although polycystins are expressed in arterial smooth muscle, the mechanism by which PKD mutations may contribute to aneurysm formation remains unclear [2, 8]. Vascular smooth muscle cells also have an altered phenotype in ADPKD. The vascular smooth muscle cell from PKD2 mutation mice responded to stimulation with increased contractile force despite a lower than normal rise in intracellular calcium concentrations. Elevated expression of contractile proteins was identified in arteries from *PKD2* haploinsufficient mice [23]. Similar results of larger contractions and lower basal cytosolic calcium concentrations were found in the aortas of mice with *PKD1* mutations [18]. There are also mechanisms proposed regarding PKD gene mutations and development and dysfunction of primary cilia in kidney tubules. Mechanosensory functions of polycystin-1 are impaired in PKD mutations and do not provoke calcium response to fluid shear stress [21]. Nauli et al. proposed polycystin-1 and polycystin-2 contribute to fluid-flow sensation and function as the same mechanotransducer [20]. Another group experimented that survivin, a chromosomal passenger, is also regulated by mechanosensory cilia and contributes to cell ploidy which results in cell polarity that underlies in the mechanism for both tubule and artery dilatation [1]. This group proposed survivin along with *PKD1*, *PKD2*, and *Tg737* mutations as a common mechanism that links between vascular and renal phenotypes in PKD [1]. Also, cultured kidney tubules from a hereditary mouse model of ADPKD contain high levels of matrix metalloproteinases [24], and kidney protein extracts from mouse ADPKD model and fluid from human renal cysts confirmed these findings [9]. These studies suggest matrix metalloproteinase might play crucial roles in extracellular matrix degradation during the formation of both renal cysts and aneurysmal disease.

There is a paucity of studies reporting outcomes of aneurysms in ADPKD patients; to our knowledge, this is one of the largest studies to investigate intracranial aneurysms in ADPKD patients. Despite the inherent shortcomings of retrospective study designs, our study is distinguishable due to the fact that follow-up was conducted in a kidney transplantation population of ADPKD patients in which end-stage renal function was normalized. The patients were included from over a broad time span between 1994 and 2018, and technical refinements and newer management protocols have improved the safety of cerebral angiography and interventional treatments for patients with renal dysfunction in ADPKD. Our retrospective analysis precludes commenting on the natural history of aneurysms and the risk factors for aneurysmal growth and rupture in ADPKD patients. Another limitation to this study is that most patients did not perform screening for PKD gene mutations, and information on family history of cerebrovascular events was unavailable. In the future, we plan to analyze genetic and molecular risk factors in a prospectively recruited group of ADPKD patients to better understand the outcomes of intracranial aneurysms in this population. We believe better assessment of the etiology, and outcomes of intracranial aneurysms in ADPKD patients would lead to screening recommendations and treatment decision guidelines.

In conclusion, intracranial aneurysms are more frequent in patients with ADPKD, and the average age of aneurysm rupture in patients with ADPKD is younger than in the general population. Endovascular treatment can be offered in selected cases, and non-invasive long-term radiological follow-up is recommended. These findings should be considered when counseling ADPKD patients on the appropriate management of intracranial aneurysms and routine screening of intracranial lesions for these patients before transplantation may be warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. This study received approval from the institutional review board of Asan Medical Center (approval number: 2019-0310).

For this type of study, formal consent is not required.

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Comments

Special high-risk subgroups are always interesting when we look for patients who will benefit from screening and treatment of UIA. This paper adds to our knowledge of the demographics and risk associated with UIA in polycystic kidney disease, ADPKD.

The authors screened with CTA, MRA, or DSA (over a 24 year period) 113 ADPKD patients for intracranial aneurysms prior to scheduled kidney transplantation. Twenty three patients (14.9%) had intracranial aneurysms with mean diameter size of 4.5 ± 2.7 mm. Nine patients (5.8%) experienced aneurysm rupture and the mean age at time of rupture was 34.9 ± 9.3 years. Twelve patients (52.2%) presented with multiple aneurysms. The most common aneurysm location was the bifurcation of the middle cerebral artery (34.9%). More than half of these patients had multiple aneurysms.

Clipping was the most common treatment in both ruptured and unruptured aneurysms, probably because of the years in which the study was done. We do not have data on clipping or endovascular treatment either before or after transplantation, nor what algorithms were used to recommend treatment.

The authors conclude that intracranial aneurysms are more frequent in patients with ADPKD and, important to consider, that the average age of intracranial artery rupture in patients with ADPKD is earlier than in the general population.

In considering this article we would ask the following further questions, with a recommendation that some of these unanswered questions form the basis for future study:

1. Is the rupture rate higher than the general UIA population? Apparently not, although rupture appears to occur at a younger age.

2. Is there a risk to performing transplant with an untreated UIA? Should aneurysms be treated before the renal transplant is done? Not discussed in this article.

3. What size are the ruptured aneurysms? Not discussed in this article.

4. What is the risk of UIA treatment in their group? Not discussed in this article.

In my personal experience unruptured aneurysm surgery in patients on dialysis has a higher risk profile, because of postoperative fluid shifts and the potential for brain edema, than in patients with normal renal function. This is a natural question for these authors to consider in future.

In my opinion this is a good article and I believe we can learn from a further analysis of this compelling group of patients.

Christopher Loftus
PA, USA