Cerebral Aneurysms in Autosomal Dominant Polycystic Kidney Disease: A Comparison of Management Approaches

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Received, January 4, 2018.

Accepted, June 23, 2018.

Published Online, July 27, 2018.

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BACKGROUND: Autosomal dominant polycystic kidney disease (ADPKD) is a risk factor for formation of intracranial aneurysms (IAs), though the ideal screening and treatment strategies in this population are unclear.

OBJECTIVE: To report outcomes of observation, open surgical, or endovascular management of ruptured and unruptured aneurysms in patients with ADPKD.

METHODS: We performed a retrospective analysis of all patients with ADPKD and IAs at a single center from 2000 to 2016.

RESULTS: Forty-five patients with ADPKD harboring 71 aneurysms were identified, including 11 patients with subarachnoid hemorrhage (SAH). Of 22 aneurysms managed with observation, none ruptured in 136 yr of clinical follow-up. Thirty-five aneurysms were treated with open surgery and 14 with an endovascular approach. Among treated aneurysms, poor neurologic outcome (modified Rankin scale >2) was seen only in patients presenting with SAH (17% SAH vs 0% elective, $P = .06$). Acute kidney injury (AKI) was also significantly associated with SAH presentation (22% SAH vs 0% elective, $P = .05$). Neither procedural complications nor AKI were associated with treatment modality. Among 175 yr of radiographic follow-up in patients with known IAs, 8 de novo aneurysms were found, including 3 that were treated. Of 11 patients with SAH, 7 ruptured in the setting of previously known ADPKD, including 2 with prior angiographic screening and 5 without screening.

CONCLUSION: Poor outcomes occurred only with ruptured presentation but were equivalent between treatment modalities. Screening is performed only selectively, and 64% (7 of 11) of patients presenting with SAH had previously known ADPKD.

KEY WORDS ADPKD, Cerebral aneurysm, Intracranial aneurysm, Polycystic kidney disease, Screening, Subarachnoid hemorrhage

Neurosurgery 84:E352–E361, 2019

DOI:10.1093/neuros/nyy336

www.neurosurgery-online.com

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent, potentially fatal monogenic disorder worldwide, with an estimated prevalence of up

to 1 in 400.^{1,2} ADPKD is associated with an increased risk of intracranial aneurysms (IAs), with 1 study finding IAs in 12% of prospectively screened patients.³ Current American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend offering noninvasive screening to all patients with ADPKD,⁴ though the Kidney Disease Improving Global Outcomes (KDIGO) conference recommends only selective screening based on the presence of other risk factors.⁵ Management options include open surgery, endovascular treatment, and observation, though studies comparing all 3 treatment options are limited. The purpose of this study was to report neurological and renal outcomes of open

ABBREVIATIONS: ADPKD, autosomal dominant polycystic kidney disease; AHA/ASA, American Heart Association/American Stroke Association; AKI, acute kidney injury; CKD, chronic kidney disease; CTA, computed tomography angiography; CT, computed tomography; ESRD, end-stage renal disease; IA, intracranial aneurysm; ICD, International Classification of Diseases; IQR, interquartile range; KDIGO, kidney disease: improving global outcomes; MCA, middle cerebral artery; MRA, magnetic resonance angiography; mRS, modified Rankin scale; SAH, subarachnoid hemorrhage

surgical, endovascular, or observational management of ruptured or unruptured aneurysms in patients with ADPKD.

METHODS

Cohort Identification

The International Classification of Diseases (ICD) codes for polycystic kidney disease (ICD-9 753.12 or 753.13, ICD-10 Q61.3 or Q61.2),⁶ intracranial aneurysm (ICD-9 437.3, ICD-10 I67.1), and subarachnoid hemorrhage (SAH; ICD-9 430, ICD-10 I60)⁷ were used to identify potential patients with both ADPKD and a ruptured or unruptured IA treated at our institution prior to 2016. After identifying 90 candidates via billing records, individual patient records were then searched using the Electronic Medical Record Search Engine to verify eligibility.⁸ ADPKD diagnosis was verified via clinical records using established age-dependent criteria for ultrasonography, renal computed tomography (CT) or magnetic resonance imaging, family history, and in some cases genetic testing.⁵ IA diagnosis was verified via reports of computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction catheter angiography (DSA).

Operative and radiological reports, clinic visit notes, and pre- and posttreatment creatinine values were reviewed for details of treatment. The following information was collected for each patient: age, sex, history of smoking, hypertension, chronic kidney disease (CKD) stage, history of renal transplant or dialysis, family history of IA or SAH, date of initial aneurysm diagnosis, diagnosis of ADPKD prior to aneurysm diagnosis, family members with ADPKD, date of first and last angiographic study (CTA, MRA, or DSA), date of last clinical follow-up, and modified Rankin scale (mRS) score at last follow-up. Aneurysm size and location, date and method of diagnosis, multiplicity of aneurysms, de novo status, and rupture status were noted for each aneurysm, with size taken from the largest recorded dimension. Basilar, vertebral, posterior inferior cerebellar, and superior cerebellar artery aneurysms were classified as posterior circulation aneurysms for this study. The institutional review board provided approval for this study with a waiver for informed consent.

Classification by Presentation Type

All SAH diagnoses were verified via clinical presentation and head CT evidence of SAH, and patients with SAH without an identifiable aneurysm were excluded. Aneurysms were classified as initial ruptured presentation if they presented in the setting of SAH and were thought by the treating physician to be the source of SAH, or as elective presentation if they presented after elective screening or were identified at the time of treatment of another aneurysm.

Classification by Treatment Methods

Aneurysms were classified by initial treatment strategy based on clinical notes at the time of discovery: open surgery, endovascular approach, or observation. Patients treated with endovascular methods were hydrated with normal saline prior to the procedure, and Isovue (Bracco, Monroe Township, New Jersey) contrast media was utilized. In those patients presenting for elective endovascular occlusion, overnight hydration and N-acetylcysteine were used preoperatively to prevent free-radical injury to the kidneys, 600 mg oral twice the day prior to the endovascular intervention, with 12 h of postprocedural saline hydration. Patients treated emergently were treated with hydration up until the time

of the procedure, followed by 12 h of postprocedural saline hydration. All in-hospital treatment was performed in consultation with experienced nephrologists.

Renal Outcomes

We used criteria for diagnosis of acute kidney injury (AKI) specified in the KDIGO AKI guidelines to assess renal outcomes when pre- and postoperative creatinine values were available.⁹ Specifically, AKI was defined as a 0.3 mg/dL or greater increase above baseline within 48 h of treatment. Detailed pre- and postoperative kidney function data were unavailable for 10 treatment sessions early in the study period, and these patients were excluded from analysis of renal function.

Procedural Complications and Neurological Outcomes

Procedural complications were classified as symptomatic or asymptomatic depending on the neurological function of the patient compared to preprocedure. Neurological outcomes at discharge and at last follow-up were identified via review of records and were dichotomized to living independently (mRS 0-2) vs dead or dependent (mRS 3-6).

Follow-on Surveillance

All subsequent radiology reports of follow-on surveillance were examined for discovery of de novo aneurysms, and all subsequent clinical encounters were examined for evidence of aneurysm rupture. Radiographic and clinical follow-ups at our institution were determined using the last known screening report for aneurysm, or the last clinic visit for any reason. Due to likely biases in patients lost to radiographic follow-up from our institution, all de novo aneurysms were reported but we were unable to calculate the incidence of their formation.

Statistical Analysis

Data were analyzed using SPSS (IBM, Armonk, New York). Continuous variables were reported using mean and range, and were evaluated using Student's *t* test; dichotomous variables were evaluated using χ^2 analysis or Fisher's exact test. Due to rightward skew within data for length of clinical and radiographic follow-up data, we reported median follow-up times along with interquartile ranges (IQR) to better describe the outliers and asymmetric distribution. All results with a probability value of less than 0.05 were considered statistically significant.

RESULTS

We identified 45 patients with ADPKD harboring 71 IAs. Demographics are shown in Table 1. There were 23 women and 22 men (mean age 49.3 yr; age range, 13-72). Thirty-five patients presented with an unruptured aneurysm. Ten patients originally presented with SAH, and 1 presented with SAH after previous discovery of a separated unruptured aneurysm. Forty (89%) had a diagnosis of hypertension at the time of aneurysm diagnosis. Thirteen had end-stage renal disease (ESRD) at the time of treatment, including 8 who had received kidney transplants.

Aneurysm characteristics stratified by type of treatment are shown in Table 2. The average sizes of ruptured, electively treated, and observed aneurysms were 7.4 mm, 5.2 mm, and

TABLE 1. Patients With ADPKD and Aneurysm Grouped by Initial Presentation

	Original presentation with rupture (n = 10 ^a)	Original presentation after screening (n = 35 ^b)	P
Age (yr)	46.2 ± 18	50.2 ± 8	.32
Female (%)	4(40)	19(54)	.42
Smoking (%)	6(60)	12(34)	.14
Hypertension (%)	9(90)	33(89)	.9
Family history SAH (%)	0(0)	4(11)	.56
Family history IA (%)	1(10)	11(31)	.25
ESRD (%) ^c	4(50)	8(28)	.39
ADPKD known at diagnosis (%)	6(60)	35(97)	.001
Size of largest aneurysm (mm)	7.5 ± 1.7	4.8 ± 2.8	.03
6-mo mRS >2	2(20)	0(0)	.04

^aIncludes one with previous negative screen.^bIncludes one who later had rupture of de novo aneurysm after positive screening for a separate aneurysm.^cRenal data unavailable for 10 patients.

3.3 mm, respectively ($P = .001$). The proportions of aneurysms in the anterior circulation in the ruptured, electively treated, and observed groups were 75%, 89%, and 95%, respectively ($P = .19$).

Presentation With SAH

Eleven patients suffered from SAH, including 1 originally diagnosed with a separate unruptured aneurysm. There was debate regarding the symptomatic aneurysm in 1 patient, as both identified aneurysms could have caused SAH. Thus, a total of 12 aneurysms were treated as presumed ruptured. Five were treated

from an endovascular approach, and 7 were treated with open surgery. Eight additional unruptured aneurysms were identified in patients who presented with rupture, either at the time of rupture or during follow-on surveillance, of which 6 received treatment (5 with open surgery and 1 with an endovascular approach). Of the 11 patients with SAH, 4 had no previous knowledge of ADPKD prior to their SAH. Seven patients carried a diagnosis of ADPKD prior to SAH and are described in Table 3. Of these 7 patients, 2 were screened previously and presented with ruptured aneurysms which were not noted on their previous screenings with MRA. The first, a 50-yr-old smoker with a history of SAH in a second degree relative, presented with rupture of a 5-mm anterior communicating artery aneurysm that was not noted on an MRA done 5 yr earlier; however at the time of rupture, repeat evaluation of the images showed the aneurysm to be present (Figure). The second, a 31-yr-old nonsmoker with no family history of aneurysms, presented with SAH from rupture of a 10-mm middle cerebral artery (MCA) aneurysm that was not reported on MRA done 3 yr earlier. The remaining 5 patients had a previous diagnosis of ADPKD but had not been screened for aneurysms. Of these 7 patients who presented with rupture in the setting of known ADPKD, only 2 had a family history of an aneurysm or SAH.

Unruptured Presentations

The remaining 59 aneurysms were found in 35 patients either through surveillance screening due to ADPKD or as small aneurysms seen intraoperatively at the time of surgery for treatment of other aneurysms ($n = 3$). All aneurysms noted through screening were brought to neurosurgical attention within months of screening, regardless of size. Of these, 37 aneurysms were treated in 25 patients, including 28 aneurysms treated with open surgery in 19 patients, and 9 aneurysms treated with an endovascular approach in 9 patients. The average size of electively treated aneurysms was 5.1 mm for patients without a personal

TABLE 2. Individual Aneurysm Characteristics Stratified by Management

	Ruptured emergency treatment (12 aneurysms in 11 patients) ^a	Unruptured/elective treatment (37 aneurysms in 25 patients)	Observation (22 aneurysms in 17 patients)	P
Size in mm (SD)	7.4 ± 1.9	5.2 ± 2.4	3.3 ± 2.2	.001
Patient age in years (SD)	47 ± 17	47 ± 12	52 ± 10	.29
Anterior circulation (%)	9(75)	33(89)	21(95)	.19
De novo since prior imaging (%)	2(17)	2(6)	7(32)	.03
ESRD (%) ^b	5(50)	6(19)	13(65)	.003
Smoking (%)	7(58)	13(35)	10(45)	.34
Family history SAH (%)	1(8)	6(16)	0(0)	.13
Family history IA (%)	2(17)	14(38)	4(18)	.17
ISUIA 2 (%)	0(0)	6(16)	3(14)	.33

^aIncludes one patient with unclear source of bleeding and two aneurysms treated.^bPre- and postoperative renal data unavailable for 10 patients.

TABLE 3. Patients With Known ADPKD Who Ruptured

Gender	Age (yr)	Hunt-Hess grade	Smoking at rupture	Family history of SAH or IA?	Family members with known ADPKD	Screening considerations	Time since previous screening MRA?	Aneurysm location	Size (mm)	Treatment	CKD stage	Outcome
F	58	4	No	None	1	CTA recommended prior to transplant but not performed	None	Basilar and internal carotid terminus	8, 9	Endovascular	5T	Discharged to home, living independently
M	50	3	Yes	IA	4	2nd degree relative with SAH; MRA read as MCA outpouching, but angiography deferred due to CKD 4 ^a	5 yr	Anterior communicating	5	Endovascular	4	Discharged to SAR, living independently
M	43	3 (5 after rerupture)	No	None	0	None	None	Vertebral	8	Endovascular	5T	Rerupture prior to endovascular treatment, death 3 mo postprocedure
M	31	3	No	None	5	None	3 yr	Middle cerebral	10	Open	5T	Tracheostomy, recovered to independence but not employed at last follow-up
M	45	4	Yes	None	1	Mother with ADPKD, siblings' history unknown	None	Anterior communicating	5	Endovascular	5	In-hospital death
F	65	1	No	IA	3	Family history of IA but no known ruptures	None	Posterior communicating	6	Open	4	Discharged home
M	59	2	Yes	None	1	No known ruptures in family	None	Anterior communicating	8	Open	4	Discharged home

^aOn retrospective review, Acomm aneurysm that subsequently ruptured was subtly apparent on previous MRA.

FIGURE. **A**, Three-dimensional (3D) reconstruction of screening magnetic resonance angiograph (MRA) with contrast of 45-yr-old with polycystic kidney disease, read as 2 mm right M1 middle cerebral artery aneurysm. **B**, Axial slice of MRA showing wisp of contrast anterior to the anterior communicating artery complex (not appreciated at the time). **C**, Noncontrast axial head CT image showing intracerebral/subarachnoid hemorrhage 5 yr later. **D** and **E**, AP projection and 3D reconstruction of right ICA angiogram demonstrating 5-mm ruptured anterior communicating artery aneurysm. **F**, After coil embolization.

TABLE 4. Treated Aneurysms Analyzed by Management

	Open surgical treatment	Endovascular treatment	P
	(35 aneurysms in 24 patients)	(14 aneurysms in 13 patients)	
Size in mm (SD)	4.8 ± 2.0	7.1 ± 2.7	.007
Patient age in years (SD)	45 ± 14	50 ± 8.0	.26
Anterior circulation (%)	34(97)	8(57)	<.001
De novo since prior imaging (%)	2(6)	2(15)	.3
ESRD (%) ^a	3(10)	9(69)	<.001
Smoking (%)	15(43)	5(36)	.75
Rupture presentation (%)	7(20)	5(36)	.25
AKI at treatment (%) ^a	1(4)	1(8)	.54
Procedural complication (%)	3(9)	2(14)	.63
Symptomatic procedural complication (%)	0(0)	2(14)	.08
6-mo mRS >2 (%)	0(0)	2(14)	.08

^aPre- and postoperative renal data unavailable for 10 patients.

history of SAH (ISUIA type I) and 4.5 mm for patients with a history of SAH (ISUIA type II; $P = .63$).¹⁰

Management With Observation

Among 22 unruptured aneurysms managed with observation in 17 patients, no ruptures were noted in 136 yr of clinical follow-up. The median size of observed aneurysms was 3 mm (range 2–10 mm), and the median clinical follow-up was 5.3 yr, (range 0.6–16 yr).

Open vs Endovascular Treatment

Thirty-three patients underwent attempted treatment of 49 aneurysms, including 14 aneurysms treated from an endovascular approach in 13 patients, and 35 aneurysms treated with open surgery in 24 patients, as described in Table 4. Aneurysms treated from an endovascular approach were larger (7.1 vs 4.8 mm, $P = .007$), more likely to be in the posterior circulation (43% vs 3%, $P < .001$), and more likely to be in patients with ESRD (69% vs 10%, $P < .001$), though 6 of the 9 ESRD patients treated from an endovascular approach had prior kidney transplants. Additionally, among treated aneurysms, we analyzed treatment modality elected by era, dividing the cohort into those treated before 2009 and those treated after. For unruptured aneurysms, there was no difference in the percentage of patients treated microsurgically with time (11/15, 73% prior to 2009 vs 17/22, 77% after 2009, $P = .78$). For ruptured aneurysms, there was a trend away from microsurgical treatment, though the numbers of patients were limited (5/7, 71% prior to 2009 vs 2/5, 40% after 2009, $P = .62$). All open surgeries involved surgical clip placement, except for a 7-mm calcified superior hypophyseal aneurysm treated with vessel wrapping due to difficult circumferential exposure. Among patients treated from an endovascular approach, 8 were treated with standard coiling, 3 with stent coiling, 1 with balloon-assisted coiling, 1 with a cardiac Magic Wallstent (Boston Scientific, Marlborough, Massachusetts) stent

for a ruptured fusiform, dissecting vertebral artery aneurysms, and 1 with a flow-diverting stent (Pipeline).

Procedural Complications

Procedural complications of treatment were classified as symptomatic and asymptomatic and are shown in Table 5. The 2 symptomatic procedural complications both occurred in patients presenting with high-grade SAH. Three previously unruptured aneurysms ruptured intraoperatively during microsurgery, including 2 separate ruptures during the same surgery. All intraoperative ruptures were managed with temporary clip placement. There were no neurological sequelae of the intraoperative ruptures, and all patients made an uneventful recovery and were discharged to home with an mRS of 0. One patient who presented with Hunt–Hess grade 4 SAH had intraoperative perforation of a ruptured anterior communicating artery aneurysm during coil embolization. His course was complicated by severe vasospasm and delayed ischemic neurological deficits, and his family elected withdrawal of care on postoperative day 5. Another patient presented with Hunt–Hess grade 4 SAH from a fusiform vertebral artery aneurysm and was treated in the subacute setting with stent placement across the neck of the aneurysm; however, the stent thrombosed shortly after placement. The patient was neurologically devastated and died 3 mo after treatment.

Renal Complications

Among patients who underwent aneurysm treatment with available pre- and postprocedure laboratory values, there were only 2 cases of AKI, both of which presented with SAH (2/9, 22% with SAH presentation vs 0% with unruptured/elective management, $P = .05$). The first was a 45-yr-old with ESRD who was scheduled to begin dialysis in the coming months. The patient was noted to have stage-1 AKI at the time of presentation with SAH from a ruptured anterior communicating artery aneurysm and died after having a repeat rupture during

TABLE 5. Procedural Complications of Treatment^a

Gender	Age (yr)	Aneurysm location	Size (mm, maximum dimension)	Morphology	Presentation	Treatment	Complication	Outcome
M	43	Vert	8	Dissecting, fusiform	SAH	Stent	Rerupture, stent thrombosis	Death at 3 mo
M	45	Acomm	5	Sacular	SAH	Coil	Intraprocedural coil perforation	In-hospital death
F	42	Pcomm, MCA	7, 2	Sacular (x2)	Screening	Clip (x2)	Intraoperative rupture of both aneurysms separately, both requiring temporary clip placement	No sequelae, discharged home 3 d postop
F	43	MCA	7	Multilobulated	Screening	Clip	Intraoperative bleeding from aneurysm requiring temporary clips	No sequelae, discharged home 3 d postop

^aFive procedural complications during treatment of five aneurysms in four patients.

TABLE 6. De novo Aneurysms

Patient	Gender	Age (yr)	Aneurysm location	Size (mm, maximum dimension)	Method of presentation	Prior IA/SAH?	Interval since last screening (yr)	Management	Clinical follow-up (yr)
1	M	52	Supraclinoid ICA	2	MRA	UIA	1	Observation	8
2	M	71	MCA	5	MRA	UIA	9	Observation	6
3	M	52	MCA	3	MRA	None	10	Observation	1
4	F	30	MCA	5	CTA	SAH	17	Clip	13
		37	MCA	2	Angiogram	SAH	2	Observation	7
		37	Acomm	2	Angiogram	SAH	2	Observation	7
		37	Supraclinoid ICA	5	Angiogram	SAH	2	Coil	7
5	M	55	Pcomm	2	MRA	UIA	11	Observation	6
6	M	50	Acomm	5	Rupture	UIA	5	Coil	4
7	M	31	MCA	10	Rupture	None	3	Clip	14
8	M	59	Cavernous ICA	2	MRA	None	8	Observation	5

coil embolization of the aneurysm. The second was a 59-yr-old woman with stage-3 CKD who underwent clip placement for a ruptured MCA aneurysm that was complicated by stage-1 AKI. This subsequently resolved prior to being discharged home.

De Novo Aneurysms, Follow-up of Patients With Known IAs

Eleven de novo aneurysms, defined as aneurysms not reported on previous imaging, were noted in 8 patients and are detailed in Table 6, including the 2 which ruptured after not being noted on screening exams (MRA with contrast) 5 and 3 yrs previously. Three patients developed de novo aneurysms after a previous negative screening and then entered the study upon identification of their aneurysms. Among 45 patients with a known diagnosis of IA, there were 175 yr of radiographic follow-up (median

1.1 yr, IQR 0-4.3) and 316 yr of clinical follow-up (median 4.8 yr, IQR 1.7-11.5) after initial diagnosis of IA. Among these patients, 8 additional de novo aneurysms were noted in 5 patients, of which 3 were treated, including a ruptured 5-mm anterior communicating artery aneurysm treated with coil embolization, an unruptured 5-mm MCA aneurysm in a patient with a history of SAH treated with clip placement, and an unruptured 7-mm supraclinoid ICA aneurysm that was treated with stent-assisted coil embolization. Though radiographic follow-up was incomplete for ADPKD patients with a known IA, and there was likely a bias towards inclusion when aneurysms were noted, we calculated a minimum annual incidence of de novo aneurysm development by assuming that patients who lacked radiographic follow-up at the time of their last clinical follow-up had no aneurysm (the most conservative assumption), resulting in a calculated

minimum incidence of de novo aneurysm development of 2.5% per yr (95% CI 1.2-4.8).

DISCUSSION

All patients who underwent elective treatment or observation had excellent outcomes. Poor neurological outcomes and AKI were associated with ruptured presentation but did not differ based on treatment type (open vs endovascular). Consistent with previous studies, we found high numbers of de novo aneurysms in ADPKD patients with IAs.¹¹⁻¹⁴ Selective screening strategies failed to prevent all ruptures, with seven patients presenting with SAH in the setting of previously known ADPKD.

Treatment Modality

Ruptured and unruptured aneurysms in patients with ADPKD are traditionally treated with open surgery. With time, increasing use of endovascular methods as well as the development of renal protective strategies has resulted in more endovascular treatments.¹⁵ Our data suggest low rates of AKI with either open or endovascular treatment, and we noted no cases of AKI in patients treated electively. However, we found relatively high rates of procedural complications in both treatment groups, in excess of what has been described for treatment of aneurysms in the general population both in our practice and in the literature in the modern era.¹⁶⁻¹⁸ Though none of the intraoperative surgical ruptures caused neurological sequelae, the relatively high rate of complications we noted may reflect especially friable, calcified vessels in this population after long-term calcium and phosphate dysregulation, a conclusion supported by other studies.^{19,20}

Despite this apparent high rate of procedural complications in ADPKD patients, the only symptomatic procedural complications in our series were associated with SAH presentations, and all of the patients treated electively were discharged home with good outcomes. The number of patients receiving microsurgical treatment in our series is somewhat higher than prevailing treatment patterns in the non-ADPKD population currently in the literature. While we saw a trend away from microsurgical treatment in the later years of our study compared to the early years for patients presenting with rupture, the number of aneurysms treated electively with microsurgery remained stably high (73% in the first era of the study compared to 77% in the later years). The overall younger age of ADPKD patients compared to the general population of aneurysm patients, a high number of patients having multiple aneurysms treated in the same setting, and a desire to avoid contrast if possible in the setting of renal disease are likely the primary factors influencing our tendency to treat with open surgery more often than may be the case in non-ADPKD patients. For IAs thought to warrant treatment, our current practice is to treat with either surgical or endovascular treatment, with a preference towards endovascular treatment

of aneurysms in the posterior circulation and in patients with high-grade hemorrhage or poor medical condition, and a preference for clip placement of wide-necked, anterior circulation aneurysms in younger patients.

Screening

Aneurysms are seen with either mutation of the genes associated with ADPKD, *PKD1* and *PKD2*,²¹ and aneurysm rupture was noted at early ages in both our study and the literature.^{22,23} The *PKD1* and *PKD2* gene products polycystin-1 and polycystin-2 both interact to regulate calcium signaling cascades, and *PKD2* mutant vascular smooth muscle cells have abnormal rates of proliferation and apoptosis, thought to account for the increased rate of aneurysm formation in ADPKD patients, especially in the context of hypertension.²⁴⁻²⁶ In contrast to a large surveillance study of ADPKD patients performed in China, which found predominantly small anterior circulation aneurysms,³ a range of aneurysm sizes and locations was noted in this study (mean size 4.7 mm, range 2-14 mm) including 8 (11%) in the posterior circulation.

Historically, early studies did not recommend screening,²⁷ though the development of noncontrast MRA prompted some to advocate for regular screening.^{28,29} Some current studies suggest only selective screening,³⁰⁻³⁴ including most prominently the KDIGO conference summary, which recommends selective screening based on the presence of other risk factors, including family history, previous rupture, high-risk professions (eg, airline pilots) and patient anxiety.⁵ A recent survey of practices in France found that most nephrologists do not advocate regular screening of this patient population.³⁵ In contrast, current American Stroke Association guidelines and other studies recommend offering noninvasive screening to all patients with ADPKD,^{4,21} with a separate study suggesting time-of-flight MRA at initial diagnosis, and follow-on surveillance at an interval from 2 to 10 yr depending on patient-specific risk factors.³⁶

As we examined only patients in whom aneurysms were discovered, we are unable to comment definitively on screening for the general ADPKD population. We do note, however, that of the 11 patients who suffered SAH from a ruptured aneurysm, 7 had known ADPKD prior to their rupture, including 5 who had not been screened, and 2 who had been screened previously but ruptured from aneurysms not previously reported. Of the 5 patients not screened, 4 had fewer than 2 known family members with ADPKD reported in their family histories, suggesting that the small numbers of ADPKD patients at risk in their families may lead to less-informed screening decisions. The failure of screening in 2 patients who had MRAs and later presented with SAH suggests the need for careful analysis of the images in patients with ADPKD, with a low threshold for further imaging if abnormalities are suggested. Given the 5 patients in the series who had no screening (in accordance with KDIGO guidelines) yet presented with SAH, offering initial universal screening as recommended by AHA/ASA guidelines appears warranted, although

the benefits must be balanced against adverse consequences and cost.

For patients with ADPKD and a known IA, we noted a de novo aneurysm development rate of at least 2.5% per year (and possibly higher with more complete radiographic follow-up), similar to previous reports of 1.3% to 4.4%,¹²⁻¹⁴ and over an order of magnitude higher than the rate reported for patients in the general population with IA.³⁷ Considering the high rate of de novo development and especially given the 2 patients in our series who presented with SAH 3 and 5 yr after previously negative screening exams, we consider ADPKD and IA an indicator for long-term and repeated screening, with a repeat scan 1 yr after the initial screening and subsequent scans based on other risk factors.

Management of small de novo aneurysms found at repeat screening remains a difficult question. Seven de novo aneurysms found at routine screening were managed nonoperatively, primarily due to their size and patient characteristics; 6 aneurysms were 3 mm or less, and the seventh was a 5-mm MCA aneurysm in a 71-yr-old dialysis patient. No de novo aneurysm managed with observation in our series ruptured over 47 cumulative years of follow-up. Given previous reports that average aneurysm size at rupture is lower in ADPKD patients¹⁴ as well as the ruptures noted in our series, in general our threshold for treatment of de novo unruptured aneurysms in ADPKD would be an aneurysm of any size in the setting of sentinel headaches, those with irregular morphology, or those exceeding 3 mm in low-risk candidates for endovascular or microsurgical treatment. A better understanding of risks factors for rupture and the genetic underpinnings of ADPKD mutations contributing to IAs may lead to more effective screening approaches and tools in the future.

Limitations

This study is a retrospective, single-center analysis with a small sample size. We analyzed only patients presenting with aneurysmal SAH or a positive screening for an IA and were unable to determine the total number patients with ADPKD screened for aneurysms. Though a seemingly high number of de novo aneurysms were noted, patients had inconsistent radiographic follow-up, and we were unable to calculate the true incidence of de novo aneurysms.

CONCLUSION

Poor neurological outcomes and AKI were noted only with ruptured aneurysms. Treatment (open surgical vs endovascular) did not affect outcome. All patients who underwent elective treatment or observation had excellent outcomes. Screening is performed only selectively, and the majority of patients presenting with SAH had previously known ADPKD.

Disclosures

This study was supported by grant NS-007222 (D.A.W.) from the National Institutes of Health. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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