Is Regular Screening for Intracranial Aneurysm Necessary in Patients with Autosomal Dominant Polycystic Kidney Disease? A Systematic Review and Meta-analysis

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Keywords

Intracranial aneurysm · Autosomal dominant polycystic kidney disease · Follow-up study · Magnetic resonance angiography

Abstract

Background: The prevalence of intracranial aneurysm in patients with autosomal dominant polycystic kidney disease (ADPKD) is higher than that among the general population. We performed a systematic review and meta-analysis on the prevalence and natural history of intracranial aneurysm among patients with ADPKD. **Methods:** Medline, Embase, Web of Science and Scopus, from inception to July 2016, were searched for studies reporting the occurrence of intracranial aneurysms among participants with ADPKD. Two authors independently assessed the eligibility of all retrieved studies and extracted data. Information on the prevalence of intracranial aneurysms and their natural history in participants with ADPKD was collected from all included studies. **Results:** Fifteen studies with 1,490 participants with ADPKD were pooled to study about the prevalence of intracranial

aneurysm in participants with ADPKD, and the prevalence rate was found to be 10% (95% CI 7–13%). Studies from China, Japan and Europe (Germany, Poland) reported a higher prevalence of intracranial aneurysm. Having a family history of haemorrhagic stroke or intracranial aneurysm was a risk factor for aneurysm occurrence. Twenty-three percent (95% CI 15–31%) of the participants had multiple aneurysms. Most of the aneurysms were small (<6 mm) and located in the anterior circulation. Five studies with 171 participants (83 with 106 aneurysms at baseline and 88 without) were analyzed to understand the natural history of aneurysms, with an incidence of aneurysm growth, new aneurysm and aneurysm rupture of 1.84% (followed up for 435 person-years), 0.57% (1,227 person-years) and 0.13% (792 person-years) respectively. **Conclusions:** Screening for intracranial aneurysm is recommended in patients with ADPKD when there is a family history of haemorrhagic stroke or intracranial aneurysm and when they are from China, Japan or Europe (Germany, Poland). Based on existing data, regular imaging follow-up is not supported. High-quality, prospective studies are needed in the future.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary diseases affecting approximately 1 in 400 to 1 in 1,000 individuals [1], and the fourth commonest cause of kidney failure globally [2]. Mutations in the PKD1 gene (located on chromosome 16, accounting for 85% of cases) or in the PKD2 gene (located on chromosome 4, accounting for 15% of cases) lead to the dysfunction of corresponding proteins (polycystin 1 and 2), resulting in fluid accumulation and cyst formation in the kidneys [1, 3]. The disease is clinically silent till adulthood with patients with PKD2 mutations having a milder phenotype than patients with PKD1 mutation.

ADPKD is associated with major extra-renal complications including the formation of cysts in other organs (liver, pancreas, seminal vesicle), cardiac valve disease and intracranial aneurysm. The prevalence of intracranial aneurysm in patients with ADPKD is higher than that among the general population (9–12 vs. 2–3%), and aneurysm rupture causing subarachnoid or intracerebral haemorrhage is among the most serious complications of ADPKD [4]. The risk factors for aneurysm growth and rupture in the general population include large size, multiple aneurysms, location (posterior circulation), irregular shape, female gender, hypertension, smoking status, prior aneurysm rupture and ethnicity [5–9]. However, little is known about the natural history of intracranial aneurysm in patients with ADPKD. This contributes to the absence of official standardized recommendations for screening for, and management of, intracranial aneurysms in patients with ADPKD. In this systematic review and meta-analysis, we provide an overview of the prevalence and natural history of intracranial aneurysms (unruptured unless specified) among patients with ADPKD.

Methods

Search Strategy

The Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement [10] was followed. The protocol was registered with PROSPERO international prospective register of systematic reviews (CRD42016046351). We searched Medline, Embase, Web of Science and Scopus databases from inception to July 2016. Our search strategy was based on the combination of the following medical subject headings terms or keywords: (“Intracranial Aneurysm” OR “Aneurysm, Ruptured” OR “aneurysm*” OR “cerebral aneurysm*”) AND (“Polycystic Kidney, Autosomal Dominant” OR “Polycystic Kidney Diseases” OR “ADPKD” OR “polycystic kidney”) (online suppl. material; for all online suppl. material, see

www.karger.com/doi/10.1159/000476073). There was no language restriction. Reference lists of all retrieved studies were cross-checked for further relevant studies until no further publications were found.

Eligibility Criteria

We included observational studies (prospective, retrospective and cross-sectional) reporting the occurrence of intracranial aneurysms among patients with ADPKD. The method of diagnosis of intracranial aneurysms was reported explicitly using imaging modalities such as magnetic resonance angiography (MRA), CT angiography, or digital subtraction angiography/cerebral angiography. We excluded the following: (1) studies with fewer than 5 ADPKD participants; (2) studies on treatment, genetics and molecular mechanisms of intracranial aneurysm; (3) studies on participants with autosomal recessive polycystic kidney disease; (4) animal studies, autopsy studies, simulation studies or mathematical models; (5) reviews, editorials, letters, conference abstracts, case or case series reports, guidelines, technical notes and book chapters.

If the same population was presented in more than one publication, the article that included the largest sample or the longest follow-up was included. We judged articles to be from the same cohort if they met the following criteria: there was evidence of overlapping recruitment sites, study dates, grant funding numbers, and similar or identical reported patient characteristics. Since we intended to explore whether screening for intracranial aneurysm and regular imaging follow-up are necessary for patients with ADPKD and mainly focused on those without neurological symptoms or history of neurological diseases, participants with a history of ruptured intracranial aneurysm, subarachnoid hemorrhage (SAH), or surgical intervention of ruptured intracranial aneurysm (endovascular coiling or neurosurgical clipping) were excluded if possible. We also excluded data from participants with the following conditions: (1) vascular malformations other than aneurysm; (2) intracranial fusiform aneurysm, dissecting aneurysm or arterial dolichoectasia. The National Institute of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies was used for the assessment of methodological quality of included studies [11].

Data Extraction

Two authors (Z.Z. and Y.X.) reviewed all retrieved articles and extracted data independently. Title and abstracts were first screened to identify potentially eligible articles, and then full texts were read to confirm inclusion. Extracted data included the following information: (1) first author, year of publication, country or region, study design, and sample size; (2) patient characteristics such as age, gender, family history of haemorrhagic stroke or intracranial aneurysm (ruptured or unruptured), hypertension, smoking status, renal dysfunction, presence of liver cyst, and proportion of patient with intracranial aneurysm in the study population; (3) aneurysm imaging characteristics such as number of aneurysms per participant, location (middle cerebral artery (MCA), anterior cerebral artery or anterior communicating artery (ACA or ACoA), internal carotid artery (ICA), anterior circulation, posterior circulation), and aneurysm size (<3, <6, 5–10, >10 mm); (4) data informing the natural history of intracranial aneurysm including follow-up imaging modality, mean or cumulative length of follow-up, number of participants over time (at recruitment, with aneurysm growth, new aneurysm or aneurysm rupture and

Fig. 1. Flowchart of literature search. IA, intracranial aneurysm.

lost to follow-up). The extracted data was cross-checked and any disagreements were resolved by discussion or in consultation with a third author (M.L.H.). We contacted the authors of the original publication for any missing data.

Statistical Analysis

The prevalence and characteristics of intracranial aneurysms in participants with ADPKD were pooled using a random-effects model. The prevalence or risk ratios were reported with 95% CIs. Similarly to previous reviews [12, 13], aneurysm was chosen as the unit of observation for analysis of location and size. For the quantitative analysis of the natural history of aneurysm during follow-up, we multiplied the number of participants by the average length of follow-up to obtain the total number of person-years of follow-up if cumulative follow-up years were not reported. To estimate the prevalence of aneurysm growth, new aneurysm or aneurysm rupture per person-years, the number of participants with subsequent aneurysm growth, new aneurysm or aneurysm rupture was divided by the total number of person-years (or cumulative follow-up years). Heterogeneity among studies was assessed using the I^2 statistics. An I^2 value of 25, 50,

and 75% was regarded as low, moderate and high heterogeneity respectively. Subgroup analysis was performed to understand the prevalence of intracranial aneurysm according to study design, region or country and whether all participants received brain imaging for intracranial aneurysm in prospective or retrospective studies. Where there was a high likelihood of differences, sensitivity analyses were performed excluding individual studies to determine reasons for the differences.

Results

Study Selection and Characteristics

We included 18 studies [14–31] in this review after excluding 4 articles with same cohorts [32–35] (Fig. 1). The full text of one included study written in Japanese [21] was translated into English by a clinical researcher at the George Institute for Global Health who comes from

Table 1. The overview of the natural history of intracranial aneurysm in participants with ADPKD in 5 included studies

Author, year	Country	Study design	Number of RP	Gender (F/M)	Mean age (std) (range)	FU length, years	Number of PL/FUP/FU IA	PYs	Number of RP with enlarged/new/ruptured IA	Percentage enlarged/new/ruptured per PYs, %
<i>ADPKD participants with IA at recruitment</i>										
Nakajima et al. [22], 2000a	Japan	P	3	2/1	49 (12) (38–62)	(M) 4.3	0/3/3	13	0/0/0	0/0/0
Belz et al. [29], 2003a	USA	P	9	3/6	44 (10) (28–53)	(M) 6.6	0/9/9	59	1/1/0	1.69/1.69/0
Irazabal et al. [27], 2011	USA	RCPCS	38	23/15	49* (29–72)	(C) 243/316 [†]	7/31/45	243/316	3 [‡] /1/0	1.23/0.41/0
Jiang et al. [30], 2013	China	P	44	23/21	53 (11)	(M) 3	4/40/49	120	4/0/0	3.3/0/0
<i>ADPKD participants without IA at recruitment</i>										
Nakajima et al. [22], 2000b	Japan	P	12	9/3	60 (14) (33–78)	(M) 4.6	0/12/0	55	0/3 [§] /1	0/5.5/1.8
Schrier et al. [31], 2004	USA	P	76	46/30	36 (7) (20–54)	(M) 9.7	0/76/0	737	0/2 /0	0/0.27/0

C, cumulative follow-up length; FU, follow-up; FUP, follow-up participants; IA, intracranial aneurysm; M, mean follow-up length; P, prospective; PL, participants lost; PYs, person-years; RCPCS, retrospective cohort with prospectively collected data; RP, recruited participants.

* Median value instead of mean.

[†] The cumulative follow-up length for enlarged or new IA was 243 years and that for ruptured IA was 316 years.

[‡] Included one new IA which increased in size from 2 to 4.4 mm during follow-up.

[§] Included one new ruptured IA with size of 2 mm during follow-up.

^{||} Included one new 4 mm IA, which was retrospectively seen on initial images and may have enlarged during follow-up.

Japan. Fifteen studies with 1,490 participants with ADPKD were analyzed for the prevalence of intracranial aneurysm (online suppl. Table I), of which 11 studies with 171 aneurysms were pooled based on aneurysm characteristics (online suppl. Table II). Five studies with 171 participants with ADPKD were analyzed to gain information on the natural history of aneurysm (Table 1). NIH quality assessment characteristics are shown in online supplementary Table III with many studies exhibiting a high risk of bias.

Results of Meta-Analysis

The pooled prevalence of intracranial aneurysm in participants with ADPKD was 10% (95% CI 7–13%) with moderate heterogeneity ($I^2 = 72\%$) (Fig. 2). The pooled prevalence of aneurysm according to aneurysm characteristics among ADPKD participants with aneurysm is shown in Table 2. Twenty-three percent (95% CI 15–31%) of participants with intracranial aneurysms had multiple aneurysms. The aneurysm location was reported for 171 aneurysms from 11 cohorts. Sixteen percent (95% CI 8–24%) of aneurysms were located in the posterior circulation, while others were located in the anterior circulation (38%, 95% CI 29–48% in MCA; 17%, 95% CI 12–23% in ACA or ACoA; 40%, 95% CI 8–72% in ICA). The aneurysm size was reported for 156 aneurysms from 8 cohorts. The pooled prevalence of aneurysm according to size was

17% (95% CI 3–31%) (for diameters <3 mm), 83% (95% CI 72–95%) (<6 mm), 28% (95% CI 16–40%) (5–10 mm) and 7% (95% CI 0–22%) (>10 mm). The risk factors for aneurysm prevalence in participants with ADPKD are shown in Table 3. Those with a family history of haemorrhagic stroke or intracranial aneurysm (ruptured or unruptured) were 2.33 (95% CI 1.60–3.38) times more likely to have an aneurysm than those without.

Four cohorts included 83 participants with ADPKD (with 106 aneurysms identified at baseline) followed for 508 person-years (Table 1). Two cohorts included 88 participants with ADPKD (without aneurysm at baseline) followed for 792 person-years. Seven participants with ADPKD (0.57% per person-years) had a new intracranial aneurysm during 1,227 person-years, including 2 (0.46%) among participants with aneurysm at baseline (followed up for 435 person-years), and 5 (0.63%) among those without aneurysm at baseline (followed up for 792 patient-years). Eight (1.84%) had aneurysms growth during 435 person-years and 1 person without aneurysm at baseline had a new ruptured aneurysm (0.13%) during 792 person-years.

Subgroup Analysis and Sensitivity Analysis

The subgroup analysis on the prevalence of intracranial aneurysm in participants with ADPKD is shown in Table 4. The pooled prevalence was highest in 2 cross-

Table 2. The pooled prevalence of intracranial aneurysm according to aneurysm characteristics

	Number of studies	Included studies (reference number)	Number of aneurysms	Prevalence, % (95% CI)	Heterogeneity I^2 , %
With multiple IA	9	14–16, 18, 21, 23, 26–28	–	23 (15–31)	13
IA location [†]					
MCA	9	14, 16, 18, 21, 23, 24, 26–28	61	38 (29–48)	29
ACA or ACoA	10	14, 16, 18, 21–24, 26–28	32	17 (12–23)	0
ICA*	11	14–16, 18, 21–24, 26–28	64	40 (8–72)	98
P-Cir	6	14, 16, 21–23, 27	14	16 (8–24)	0
IA size (mm) [‡]					
<3	5	16, 18, 26–28	34	17 (3–31)	90
<6	8	16, 18, 21–23, 26–28	124	83 (72–95)	83
5–10	8	16, 18, 21–23, 26–28	39	28 (16–40)	61
>10	2	23, 26	3	7 (0–22)	50

ACA or ACoA, anterior cerebral artery or anterior communicating artery; IA, intracranial aneurysm; ICA*, internal carotid artery (including the junction between internal carotid artery and posterior communicating artery); MCA, middle cerebral artery; P-Cir, posterior circulation.

[†] Eleven studies with 171 IA were included for analysis of location.

[‡] Eight studies with 156 IA were included for analysis of size. Total IA is more than 156 because of partial overlap between size <6 and 5–10 mm.

Fig. 2. Meta-analysis of the prevalence of intracranial aneurysm in participants with ADPKD by years of publication.

sectional studies from Japan (39%, 95% CI 8–70%). The pooled prevalence was lower in retrospective studies than in prospective studies (4%, 95% CI 1–6% vs. 11%, 95% CI 8–14%). For prospective studies, the prevalence of intracranial aneurysm in Europe (Germany, Poland) (16%,

95% CI 9–22%) and Asia (Japan, China) (17%, 95% CI 8–26%) was higher than that in the United States (8%, 95% CI 4–11%). One of the 3 retrospective studies and all studies with prospective recruitment performed brain imaging for intracranial aneurysm in all participants,

Table 3. Risk ratio of intracranial aneurysm presence in participants with ADPKD

	Number of studies	Included studies (reference number)	Risk ratio (95% CI)	Heterogeneity I^2 , %
Gender				
Female	11	14–16, 18, 21–24, 26–28	Reference	–
Male	11	14–16, 18, 21–24, 26–28	1.13 (0.82–1.55)	0
Age, years				
<40	4 (5)	16, 22, 26–28	Reference	–
40–59	4	22, 26–28	1.88 (0.98–3.63)	7
≥40	5	16, 22, 26–28	2.07 (0.79–5.40)	53
≥60	4	22, 26–28	1.88 (0.52–6.70)	63
FH	6	15, 16, 18, 22, 26, 27	2.33 (1.60–3.38)	0
Hypertension	5	14, 18, 21, 26, 28	0.86 (0.53–1.39)	0
Smoking*	1	27	1.12 (0.61–2.05)	–
Renal dysfunction	4	18 [†] , 21 [‡] , 26 [†] , 28 [§]	1.45 (0.92–2.28)	0
Liver cyst	2	18, 26	1.06 (0.60–1.89)	9

FH, family history of haemorrhagic stroke or intracranial aneurysm (ruptured or un-ruptured).

* Participants with smoking history or smoking at the time of recruitment.

[†] The definition of renal dysfunction was not specified in text.

[‡] Chronic renal failure on haemodialysis or predialysis (serum creatinine ≥2 mg/dL) was considered renal dysfunction.

[§] Stages 3 to 5 of chronic kidney disease were considered renal dysfunction.

Table 4. Subgroup analysis for the prevalence of intracranial aneurysm in participants with ADPKD

	Number of studies	Included studies (reference number)	Number of participants with ADPKD	Pooled prevalence, % (95% CI)	Heterogeneity I^2 , %
Study design					
Prospective and RCPCS	10	14, 16, 18, 21–24, 26–28	1,177	11 (8–14)	59
Retrospective	3	17, 19, 25	297	4 (1–6)	10
Cross-sectional	2	15, 20	16	39 (8–70)	38
Region or country (Prospective and RCPCS)					
USA	3	16, 18, 27	592	8 (4–11)	50
Europe (Germany, Poland)	2	23, 28	126	16 (9–22)	0
Asia (Japan, China)	4	14, 21, 22, 26	417	17 (8–26)	52
Brain imaging in all participants (prospective, RCPCS and Retrospective)					
Yes	11	14, 16*, 17, 18, 21–24, 26–28	1,248	10 (8–13)	51
No or NR	2	19, 25	222	3 (1–5)	0

NR, not reported; RCPCS, retrospective cohort with prospectively collected data.

* Four of 92 participants were excluded from analyses because of incomplete IA screening due to technical failure or occurrence of adverse reactions.

with the pooled prevalence of 10% (95% CI 8–13%). Sensitivity analyses were performed on the prevalence of aneurysm located in the ICA and with small size (<3, <6 mm; online suppl. Table IV). After removing 2 studies (one with all 4 detected aneurysms located in the ICA, the other with only 1 out of the 18 aneurysm located in the ICA) [15, 28], the prevalence of aneurysm located in the

ICA was 39% (95% CI 30–47%) with low heterogeneity ($I^2 = 6\%$). After removing one study with all 8 detected aneurysms with size <6 mm [16], the prevalence of aneurysm with size <6 mm was 81% (95% CI 73–89%) with low heterogeneity ($I^2 = 19\%$). The heterogeneity for the prevalence of aneurysm with size <3 mm was still high in sensitivity analyses.

Discussion

Our systematic review showed that the prevalence of intracranial aneurysm in patients with ADPKD was 10% (95% CI 7–13%). Having a family history of haemorrhagic stroke or intracranial aneurysm (ruptured or unruptured) was the only factor associated with a significantly higher prevalence of intracranial aneurysm in patients with ADPKD. While there was an elevated prevalence of aneurysm in participants ≥ 40 years of age, male and with renal dysfunction, this was not statistically significant. Being hypertensive, smoking and having liver cysts had no effect on the prevalence of aneurysm, but the results for the latter 2 should be treated with caution due to the small number of cohorts.

We included more cohorts in our review than 2 previous systematic reviews [12, 13]. Two studies [36, 37] (included in Vlak et al. [12]) were excluded from our review because the diagnosis of aneurysm was based on autopsy or surgery. Another [38] was excluded because the study population included families rather than individual patients with ADPKD. Our pooled prevalence was consistent with Rinkel et al. [13] (10%, 95% CI 6.2–15%), but more precise (narrower CI). The heterogeneity among studies of prevalence was moderate. Two retrospective studies [19, 25] may have underestimated the prevalence of aneurysm, since brain imaging may not have been completed for all participants. In prospective studies, there may have been a bias towards recruiting participants with suspected aneurysm or a high risk of developing one. In all prospective and cross-sectional studies, the prevalence was higher in participants with ADPKD from Asia and Europe than that from the United States, which may indicate geographic or population difference.

Most of the aneurysms in our systematic review were located in the anterior circulation, consistent with Vlak et al. [12] results in the general population (18% in ACA and branches, 35% in MCA). However, there was high heterogeneity for the prevalence of aneurysm located in the ICA. The extreme results of one small study from Japan [15] and one prospective study from Poland [28] accounted for some of the heterogeneity. Small aneurysms (< 6 mm) were more prevalent among patients with ADPKD than in the general population (72%, 95% CI 68–77) [13]. The sources of heterogeneity for the prevalence of tiny aneurysms (< 3 mm) remain unclear. In our opinion, the improvements in imaging technology over the years may have enhanced the capability of detecting intracranial aneurysm. In addition, different imaging modalities adopted among studies may have also affected the detection of tiny aneurysms.

To the best of our knowledge, this is the first systematic review on the natural history of intracranial aneurysm in patients with ADPKD. Compared to the general population [5, 6], a smaller proportion of aneurysm grow or rupture (growth: 1.84% per person-years in patients with ADPKD vs. 9% per person-years in general population; rupture: 0.13 vs. 0.6–1.3% per person-years). The sole ruptured aneurysm in our review was from a 33-year-old man with negative MRA at recruitment, who developed SAH at 10 months due to rupture of a 2-mm saccular aneurysm [22]. The risk of developing a new aneurysm during follow-up was also low, making frequent imaging follow-up unnecessary for patients with ADPKD and intracranial aneurysm.

This systematic review has the following limitations: (1) the lack of individual participants' data did not allow us to conduct multivariable analyses on the risk factors for intracranial aneurysm presence; (2) the limited number of studies (5) on the natural history of intracranial aneurysm is not enough for management recommendations and assessment of risk factors for aneurysm growth, new aneurysm or aneurysm rupture; (3) full texts were not available for 5 articles and 2 of the 5 articles were not written in English, which might introduce potential bias.

Based on our systematic review, screening for aneurysm in patients with ADPKD is more relevant when there is a family history of haemorrhagic stroke or intracranial aneurysm (ruptured or unruptured), and when patients are from China, Japan or Europe (Germany, Poland). Regular imaging follow-up is not recommended due to a low prevalence of aneurysm growth, new aneurysm and aneurysm rupture. Since existing data on the natural history of intracranial aneurysm in patients with ADPKD is limited, additional high-quality, prospective studies are needed to develop management recommendations.

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Disclosure Statement

None.

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